

PCT/INT'L COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 10242-20	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/CA 99/00250	International filing date (day/month/year) 25/03/1999	(Earliest) Priority Date (day/month/year) 26/03/1998
Applicant UNIVERSITY OF SASKATCHEWAN TECHNOLOGIES INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of **8** sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of invention is lacking (see Box II).

4. With regard to the title,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the abstract,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 99/00250

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims: 1-25 (all part) Compounds according to formula (I) wherein $n = 1$
2. Claims: 1-25 (all part) Compounds according to formula (I) wherein $n = 2$
3. Claims: 1-25 (all part) Compounds according to formula (I) wherein $n = 3$

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1 to 6, 10 to 17, 20 to 25, 26 (all in part)

Claim 1 is unclear, since the subject-matter of claim 1, which includes the subject-matter of the dependent claim 5, does not contain the disclaimers of claim 5. Therefore all the compounds disclaimed in claim 5 are novelty destroying for the subject-matter of claim 1 as well as for the claims 2 to 4 and 6.

It is stressed that the scope of claim 6 is broader than the scope of claim 1, because the substituent R1 could be substituted.

Claim 5 contains so many provisos that a lack of clarity and conciseness within the meaning of Art. 6 PCT arises to such extent as to render a meaningful search of the claims impossible.

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims (claims 1-4 and 6 for instance) may be said to define subject-matter for which protection might legitimately be sought (Art. 6 PCT).

For all these reasons, a meaningful search over the hole breadth of the claims is impossible. Consequently, the search has been restricted to claims 7, 8, 9, 18, 19, 23.

Claim 26 discloses a commercial package, which is defined by the use of the pharmaceutical composition contained in it and not by features of the package itself.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 99/00250

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6	C07C229/12	C07C255/24	C07C255/25	C07F9/38	C07F9/40
	C07D257/04	A61K31/195	A61K31/215	A61K31/275	A61K31/66

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07F C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 97 45115 A (TROPHIX PHARM INC) 4 December 1997 (1997-12-04)</p> <p>page 23 -page 28; claims 1,24 ---</p>	1,6, 10-17, 20-22, 24,25
X	<p>WO 92 15551 A (UNIV SASKATCHEWAN) 17 September 1992 (1992-09-17) claims 1,30 ---</p> <p>---</p>	1-5,26

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- °A° document defining the general state of the art which is not considered to be of particular relevance
- °E° earlier document but published on or after the international filing date
- °L° document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- °O° document referring to an oral disclosure, use, exhibition or other means
- °P° document published prior to the international filing date but later than the priority date claimed

- °T° later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- °X° document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- °Y° document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- °&° document member of the same patent family

Date of the actual completion of the international search

12 November 1999

Date of mailing of the international search report

26. NOV. 1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Rufet, J

INTERNATIONAL SEARCH REPORT

National Application No

PCT/CA 99/00250

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KUNIKO NISHIMURA ET AL.: "Inactivation of monoamine oxidase B by analogues of the anticonvulsant agent milacemide (2-(n-pentylamino)acetamide)" JOURNAL OF MEDICINAL CHEMISTRY., vol. 36, no. 4, 1993, pages 446-448, XP002109875 WASHINGTON US page 447, column 2 -page 448, column 1 ---	1-7, 9
X	DE 41 00 856 A (KOREA INST SCIENCE TECHNOLOGY) 2 October 1991 (1991-10-02) examples 1-6 ---	1-6
X	DE 11 39 738 B (GENERAL ANILINE & FILM CORPORATION) 15 November 1962 (1962-11-15) page 14; table II ---	1-6
X	DE 20 52 256 A (CILAG CHEMIE AG) 6 May 1971 (1971-05-06) page 23; example 29 ---	1-6
X	DE 24 42 239 A (SUMITOMO CHEMICAL CO) 13 March 1975 (1975-03-13) * page 2, compound 8 * ---	1-6
X	DE 25 55 769 A (BASF AG) 16 June 1977 (1977-06-16) example 5 ---	1-6
X	DE 15 67 221 A (VEB BERLIN-CHEMIE) 16 April 1970 (1970-04-16) page 2 -page 4 ---	1-6
A	WO 96 05286 A (FRONTIER KK) 22 February 1996 (1996-02-22) abstract ---	1, 20-25
X	CHEMICAL ABSTRACTS, vol. 55, no. 15, 1961 Columbus, Ohio, US; abstract no. 14441b, GERHARD SATZINGER: "5-Substituted and 1,5-condensed tetrazoles." page 14441; column 1; XP002109056 abstract & ANN., vol. 638, 1960, pages 159-173, ---	1-6
		-/-

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00250

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FREDERICK LEONARD ET AL.: "Potential antiviral agents." JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 78, no. 6, 20 March 1956 (1956-03-20), pages 1199-1201, XP002109053 DC US page 1199; table I ---	1-6
X	HANS-G. BOIT: "BEILSTEINS HANDBUCH DER ORGANISCHEN CHEMIE, 4. Edition, 3. suppl., vol. 4, part 2" 1963, SPRINGER-VERLAG XP002109054 page 1137, paragraph 9 ---	1-6
X	REINER LUCKENBACH: "BEILSTEINS HANDBUCH DER ORGANISCHEN CHEMIE, 4. Edition, 4. suppl., vol. 4, part 3" 1980, SPRINGER-VERLAG XP002109055 page 2386, paragraph 3 ---	1-6
X	SHIGEYOSHI MIYAGISHI ET AL.: "Phase transition of N-acyl amino acids with different acyl group" BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN., vol. 59, no. 2, 1986, pages 557-562, XP002109876 JAPAN PUBLICATIONS TRADING CO. TOKYO., JP ISSN: 0009-2673 page 557; table 1 ---	1-6
X	FR 2 451 913 A (CONTINENTAL PHARMA) 17 October 1980 (1980-10-17) claims 1,15; example 5 ---	1-6, 9-12
X	CHEMICAL ABSTRACTS, vol. 92, no. 23, 1980 Columbus, Ohio, US; abstract no. 192462W, KIRINO, OSAMU ET AL.: "Studies on anti-fusarium disease activity of aminonitrile derivatives....." page 167; column 2; XP002122173 abstract & AGRIC. BIOL. CHEM., vol. 44, no. 1, 1980, pages 31-34, ---	1-6, 9-12
		-/-

INTERNATIONAL SEARCH REPORT

National Application No

PCT/CA 99/00250

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOSEPH CORSE ET AL.: "N-substituted 2-methoxy-6-chloro-9-aminoacridines derived from unsymmetrical aliphatic amines" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 68, 1946, pages 1905-1910, XP002122172 DC US table II ---	1-6, 9
X	CHEMICAL ABSTRACTS, vol. 74, no. 8, 1971 Columbus, Ohio, US; abstract no. 32910r, ISHIZUKA, TETSUO ET AL.: "Alkyl-beta-amines from long-chain olefins" page 70; column 1; XP002122174 abstract & CHIM. PHYS. APPL. PRAT. AG. SURFACE, C. R. CONGR. INT. DETERG., 5TH, vol. 1, 1968, pages 183-191, ---	1-6
X	CHEMICAL ABSTRACTS, vol. 55, no. 8, 1961 Columbus, Ohio, US; abstract no. 7275d, SEIZABURO SAKAKIBARA ET AL.: "Cationic surface-active agents from long-chain alkyl amines and acrylonitrile" page 7275; column 1; XP002122175 abstract & YUKAGAKU, vol. 6, 1957, pages 263-266, ---	1-6
X	CHEMICAL ABSTRACTS, vol. 55, no. 15, 24 July 1961 (1961-07-24) Columbus, Ohio, US; abstract no. 14441b, GERHARD SATZINGER: "5-substituted and 1,5-condensed tetrazoles." page 14441; column 1; XP002122176 abstract & ANN., vol. 638, 1960, pages 159-173, --- -/-	1-6

INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CHEMICAL ABSTRACTS, vol. 55, no. 23, 13 November 1961 (1961-11-13) Columbus, Ohio, US; abstract no. 23837e, HISASHI TAKAHASHI: "Effects of derivatives of gamma-aminobutyric acid " page 23837; column 1; XP002122177 abstract & NIPPON SEIRIGAKU ZASSHI, vol. 23, 1961, pages 417-425, ---</p>	1-6
X	<p>US 4 548 726 A (MORRIS-SHERWOOD BETTY J ET AL) 22 October 1985 (1985-10-22) abstract ---</p>	1-6
X	<p>US 3 991 208 A (DUDZINSKI ZDZISLAW W ET AL) 9 November 1976 (1976-11-09) abstract -----</p>	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 99/00250

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9745115	A	04-12-1997	AU 3153097 A CA 2254833 A NO 985711 A	05-01-1998 04-12-1997 07-12-1998
WO 9215551	A	17-09-1992	US 5169868 A AT 173459 T AU 658611 B AU 1323692 A CA 2105171 A DE 69227627 D DE 69227627 T EP 0573498 A JP 6505241 T US 5508311 A	08-12-1992 15-12-1998 27-04-1995 06-10-1992 02-09-1992 24-12-1998 24-06-1999 15-12-1993 16-06-1994 16-04-1996
DE 4100856	A	02-10-1991	JP 1877781 C JP 3279390 A JP 6004658 B US 5099056 A	07-10-1994 10-12-1991 19-01-1994 24-03-1992
DE 1139738	B		GB 912266 A	
DE 2052256	A	06-05-1971	AT 302348 B BE 758165 A DK 324975 A ES 384946 A FR 2070171 A GB 1287317 A NL 7015825 A SE 356044 B CH 543487 A DK 131933 B JP 49048548 B JP 50026541 B US 3703537 A US 3755415 A US 3786056 A	15-09-1972 28-04-1971 20-10-1975 01-09-1973 10-09-1971 31-08-1972 03-05-1971 14-05-1973 14-12-1973 29-09-1975 21-12-1974 01-09-1975 21-11-1972 28-08-1973 15-01-1974
DE 2442239	A	13-03-1975	JP 956306 C JP 50101525 A JP 53033657 B JP 50101526 A JP 946802 C JP 50101530 A JP 53022144 B JP 910778 C JP 50105825 A JP 52041330 B JP 850757 C JP 50049420 A JP 51024569 B AU 475364 B DK 467874 A FR 2242374 A NL 7411789 A AU 7301774 A US 3966789 A ZA 7405500 A	31-05-1979 12-08-1975 16-09-1978 12-08-1975 30-03-1979 12-08-1975 06-07-1978 14-06-1978 20-08-1975 18-10-1977 19-03-1977 02-05-1975 24-07-1976 11-03-1976 05-05-1975 28-03-1975 07-03-1975 11-03-1976 29-06-1976 28-04-1976

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 99/00250

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
DE 2555769	A 16-06-1977	BE 848353 A		16-05-1977
		CH 628325 A		26-02-1982
		FR 2334666 A		08-07-1977
		GB 1560549 A		06-02-1980
		US 4113764 A		12-09-1978
DE 1567221	A 16-04-1970	FR 1455235 A		30-12-1966
		GB 1048507 A		
WO 9605286	A 22-02-1996	JP 8056655 A		05-03-1996
		EP 0723583 A		31-07-1996
		US 5792479 A		11-08-1998
FR 2451913	A 17-10-1980	LU 81068 A		08-10-1980
		LU 81069 A		08-10-1980
		AT 381302 B		25-09-1986
		AT 154680 A		15-02-1986
		AT 391134 B		27-08-1990
		AT 275084 A		15-02-1990
		AT 392271 B		25-02-1991
		AT 275184 A		15-08-1990
		AU 536499 B		10-05-1984
		AU 5678480 A		25-09-1980
		CA 1184567 A		26-03-1985
		CH 645091 A		14-09-1984
		DE 3010599 A		09-10-1980
		DE 3050800 C		22-06-1989
		DK 123580 A, B,		23-09-1980
		ES 490536 A		16-04-1981
		FI 800900 A, B,		23-09-1980
		GB 2048852 A, B		17-12-1980
		GR 68005 A		26-10-1981
		IE 49751 B		11-12-1985
		IL 59679 A		30-11-1984
		JP 1462820 C		28-10-1988
		JP 55143944 A		10-11-1980
		JP 63009491 B		29-02-1988
		NL 8001721 A, B,		24-09-1980
		NO 800830 A		23-09-1980
		PT 70992 A		01-04-1980
		SE 453917 B		14-03-1988
		SE 8002204 A		23-09-1980
		US 4639468 A		27-01-1987
		ZA 8001682 A		26-08-1981
US 4548726	A 22-10-1985	NONE		
US 3991208	A 09-11-1976	US 3974208 A		10-08-1976

RECD 29 AUG 2000	
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 10242-20	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CA99/00250	International filing date (day/month/year) 25/03/1999	Priority date (day/month/year) 26/03/1998	
International Patent Classification (IPC) or national classification and IPC C07C229/12			
Applicant UNIVERSITY OF SASKATCHEWAN TECHNOLOGIES INC.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of **6** sheets, including this cover sheet.
 - This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 14/10/1999	Date of completion of this report 28.07.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Grammenoudi, S Telephone No. +49 89 2399 8324



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA99/00250

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-38 as originally filed

Claims, No.:

1-24 as received on 19/06/2000 with letter of 19/06/2000

2. The amendments have resulted in the cancellation of:

the description, pages:
 the claims, Nos.:
 the drawings, sheets:

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

the entire international application.
 claims Nos. 17-23,24.

because:

the said international application, or the said claims Nos. 17-23 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA99/00250

see separate sheet

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 24 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-23
	No: Claims
Inventive step (IS)	Yes: Claims 5-7,13-15,21
	No: Claims 1-4,8-12,16-20,22-23
Industrial applicability (IA)	Yes: Claims 1-16
	No: Claims

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

SECTION III

1. Claim 24 discloses a commercial package, which is defined by the use of the pharmaceutical composition contained in it and not by the features of the package itself. Therefore an examination of such a claim cannot be carried out.
2. Claims 17-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

For the assessment of these claims on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

INVENTION A

The examination is being carried out on the basis of present claims 1-23 wherein n is 1 in formula I.

D2= WO-A-92/15551

1. The present application relates to aliphatic amino derivatives for use as cellular rescue agents.
2. Document D2, which is considered to represent the closest state of the art, discloses aliphatic propargylamines for the treatment of neurodegenerative disorders in mammals such as Alzheimer's disease, Parkinson's disease, Huntington's disease and stroke (see D2, paragraph bridging pages 22 and 23). It is believed that these disorders involve apoptotic processes.

3. The problem to be solved by the present application with respect to D2 is seen in the provision of alternative compounds usable as cellular rescue agents for the treatment and prevention of diseases in which cell death occurs by apoptosis.
4. The compounds of present claims 1-10 differ from the propargyl amines known from D2 in that the group X cannot be alkynyl. These compounds, their use (claims 17-23) as well as compositions (claims 11-16) comprising them, are therefore novel. Some compounds involved in claims 17-23 are known from the prior art but not their use for the claimed purpose. Accordingly, the subject-matter of claims 1-23 meets the requirements of Article 33(2) PCT.
5. The above technical problem can only be regarded as having been solved if, in deciding the issue under Article 33(3) PCT, it would be credible that all compounds within the scope of present claims 1-4 are useful as cellular rescue agents. It is stated, however, in the description on pages 3 and 8 that for a particular class or subclass of the claimed compounds the inactive enantiomer does not prevent apoptosis but can antagonize the antiapoptotic actions of the active enantiomers. Indeed, the biological data according to Example 1 clearly show that a number of individual compounds falling within the scope of present claims 1-4 does not exhibit antiapoptotic properties at all (cf. Tables 1-4) and hence does not solve the problem posed.

It is also obvious from Tables 1-4 that even minor structure changes can lead to a total loss of antiapoptotic activity. For instance, whereas (R)-2-(2-pentylamino)acetonitrile is active and (R)-2-(2-heptylaminoo)acetonitrile inactive, (S)-2-(2-pentylamino)acetonitrile is inactive and (S)-2-(2-heptylaminoo)acetonitrile active (cf. Table 4). Apparently, reliable predictions concerning the influence of structural changes and chirality of the claimed compounds on their antiapoptotic properties are not possible.

It should be also noted that from the vast number of possible meanings for R, only some few examples of alkyl groups are presented in the biological examples. Thus, taking into account the broad definition of claims 1-4 as compared to the very narrow structural range of the compounds tested in Example 1, it is inherently unlikely that all remaining compounds claimed possess the alleged antiapo-

ptotic properties.

The compounds according to claims 1-4, their use for the treatment or prevention of a disease in which cell death occurs by apoptosis as well as the compositions comprising these compounds are therefore regarded as not involving an inventive step. Accordingly, the subject-matter of claims 1-4, 8-12, 16-20 and 22-23 does not satisfy the requirements of Article 33(3) PCT.

6. The antiapoptotic activity of the individual compounds according to the remaining claims is considered to be credible. Claims 5-7, 13-15 and 21 therefore meet the requirements of Article 33(3) PCT.

SECTION VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D2 is not mentioned in the description, nor is this document identified therein.

SECTION VIII

1. The term "lower" in connection with acyloxy (cf. claims 1, 11 and 17) is unclear since the upper limit to the number of C-atoms is not defined (Art. 6 EPC).

INVENTION B

The examination is being carried out on the basis of present claims 1-23 wherein n is 2 in formula I.

D2= WO-A-92/15551

1. The present application relates to aliphatic amino derivatives for use as cellular rescue agents.

2. Document D2, which is considered to represent the closest state of the art, discloses aliphatic propargylamines for the treatment of neurodegenerative disorders in mammals such as Alzheimer's disease, Parkinson's disease, Huntington's disease and stroke (see D2, paragraph bridging pages 22 and 23). It is believed that these disorders involve apoptotic processes.
3. The problem to be solved by the present application with respect to D2 is seen in the provision of alternative compounds usable as cellular rescue agents for the treatment and prevention of diseases in which cell death occurs by apoptosis.
4. The compounds of present claims 1-10 differ from the propargyl amines known from D2 in that the group X cannot be alkynyl. These compounds, their use (claims 17-23) as well as compositions (claims 11-16) comprising them are therefore novel. Some compounds involved in claims 17-23 are known from the prior art but not their use for the claimed purpose. Accordingly, the subject-matter of claims 1-23 meets the requirements of Article 33(2) PCT.
5. The above technical problem can only be regarded as having been solved if, in deciding the issue under Article 33(3) PCT, it would be credible that all compounds within the scope of present claims 1-4 are useful as cellular rescue agents. It is stated, however, in the description on pages 3 and 8 that for a particular class or subclass of the claimed compounds the inactive enantiomer does not prevent apoptosis but can antagonize the antiapoptotic actions of the active enantiomers. Indeed, the biological data according to Example 1 clearly show that a number of individual compounds falling within the scope of present claims 1-4 does not exhibit antiapoptotic properties at all (cf. Tables 1-4) and hence does not solve the problem posed.

It is also obvious from Tables 1-4 that even minor structure changes can lead to a total loss of antiapoptotic activity. For instance, while (R)-3-(2-heptylaminoo)propionic acid is active as a cellular rescue agent, the 2-pentyl homologue is not (cf. Table 1). In striking contrast to this, R-2-(2-pentylamino)ethane phosphonic acid is active (cf. Table 2). Apparently, reliable predictions concerning the influence of structural changes and chirality of the claimed compounds on their antiapoptotic properties are not possible.

It should be also noted that from the vast number of possible meanings for R, only some few examples of alkyl groups are presented in the biological examples. Thus, taking into account the broad definition of claims 1-4 as compared to the very narrow structural range of the compounds tested in Example 1, it is inherently unlikely that all remaining compounds claimed possess the alleged antiapoptotic properties.

The compounds according to claims 1-4, their use for the treatment or prevention of a disease in which cell death occurs by apoptosis as well as the compositions comprising these compounds are therefore regarded as not involving an inventive step. Accordingly, the subject-matter of claims 1-4, 8-12, 16-20 and 22-23 do not satisfy the requirements of Article 33(3) PCT.

6. The antiapoptotic activity of the individual compounds according to the remaining claims is considered to be credible. Claims 5-7, 13-15 and 21 therefore meet the requirements of Article 33(3) PCT.

SECTION VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D2 is not mentioned in the description, nor is this document identified therein.

SECTION VIII

1. The term "lower" in connection with acyloxy (cf. claims 1, 11 and 17) is unclear since the upper limit to the number of C-atoms is not defined (Art. 6 EPC).

PATENT COOPERATION TREATY

PCT

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International application No.	Applicant's or agent's file reference
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International filing date (day/month/year)	Priority date (day/month/year)
25 March 1999 (25.03.99)	26 March 1998 (26.03.98)

Applicant
DYCK, Lilian, E. et al

1. The designated Office is hereby notified of its election made:

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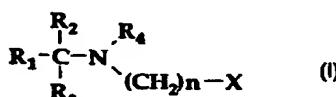
made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(57) Abstract

Novel compounds of formula (I) are described wherein: $\text{R}_1=(\text{CH}_2)_m\text{CH}_3$ where m is 0 or an integer in the range from 1 to 16, or an alkenyl, alkynyl, alkoxy, alkylthio, or alkyl sulfinyl group having from 2 to 17 carbon atoms; $\text{R}_2=\text{H}$, CH_3 or CH_2CH_3 ; $\text{R}_3=\text{H}$ or CH_3 ; $\text{R}_4=\text{H}$ or CH_3 ; $\text{R}_5=\text{lower alkyl}$ having from 1 to 5 carbon atoms; n is an integer in the range from 1 to 3, and X is carboxyl (COOH) or carbalkoxy (COOR_5), cyano ($\text{C}\equiv\text{N}$), phosphonic acid (PO_3H_2), phosphonate ester ($\text{PO}_3[\text{R}_5]_2$) or 5-tetrazole, and pharmaceutically acceptable salts thereof. Preferably, the compounds are optically pure enantiomers of the R- or S-configuration in which $\text{R}_3=\text{R}_4=\text{R}_5=\text{H}$, $\text{R}_2=\text{CH}_3$ and R_1 is a saturated aliphatic chain of one to five carbon atoms. The compounds are useful as cellular rescue agents.

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Title: ALIPHATIC AMINO CARBOXYLIC AND AMINO PHOSPHONIC ACIDS, AMINO NITRILES AND AMINO TETRAZOLES AS CELLULAR RESCUE AGENTS

FIELD OF THE INVENTION

5 The invention relates to novel aliphatic amino carboxylic and amino phosphonic acids, amino nitriles and amino tetrazoles, their salts, compositions containing such compounds and to the use of such compounds as cellular rescue agents in human and veterinary medicine.

BACKGROUND OF THE INVENTION

10 Neurodegenerative disorders (for example, chronic disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, Pick's disease, amyotrophic lateral sclerosis and glaucoma as well as acute injuries like stroke, head trauma, Bell's palsy and spinal cord injuries) are now believed to involve apoptotic processes.

15 Deprenyl, the aliphatic propargylamines, their respective desmethyl analogues and rasagiline have been shown to protect and rescue damaged neurons in several models of degeneration [1-16]. The propargyl group was thought to be a requirement for the protective or rescuing activity of these drugs. Previous studies have examined the
20 N-demethylation and/or depropargylation of these drugs [7, 17].

It has been known for some time that some aliphatic and aromatic acetylenic compounds react with P450 enzymes. One of these reactions results in oxidation of the terminal carbon of the acetylenic functional group to form the corresponding acid [18-20]. The possibility of
25 oxidation of the N-acetylene group of the aliphatic propargylamines to form carboxylic acid metabolites has not been previously addressed. The potential of related acidic compounds (the amino phosphonic acids and amino tetrazoles) and precursors to such compounds (amino nitriles and amino esters) as antiapoptotic agents had also not been previously
30 considered.

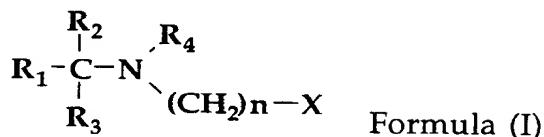
The present inventors have found that aliphatic amino carboxylic and amino phosphonic acids, amino nitriles and amino

- 2 -

tetrazoles are antiapoptotic agents and may be useful as cellular rescue agents in human and animal treatments.

SUMMARY OF THE INVENTION

The present invention relates to a compound of the general
5 formula (I),



wherein:

R₁ is (CH₂)_mCH₃ where m is 0 or an integer in the range from 1 to 16, or an
10 alkenyl, alkynyl, alkoxy, alkylthio, or alkyl sulfinyl group having from 2 to
17 carbon atoms. R₁ may be unsubstituted or substituted with at least one
of the substituents selected from hydroxy, aldehyde, oxo, lower acyloxy,
halogen, thio, sulfoxide, sulfone, phenyl, halogen-substituted phenyl,
hydroxy-substituted phenyl, cycloalkyl having from 3 to 6 carbon atoms
15 and heterocyclic substituents having between 3 and 6 atoms, of which
from 1 to 3 are heteroatoms selected from O, S and/or N,

R₂ = H, CH₃ or CH₂CH₃,

R₃ = H or CH₃,

R₄ = H or CH₃,

20 R₅ = lower alkyl having from 1 to 5 carbon atoms,

n is an integer in the range from 1 to 3,

and X is carboxyl (COOH), carbalkoxy (COOR₅), cyano (C≡N), phosphonic
acid (PO₃H₂), phosphonate ester (PO₃[R₅]₂) or 5-tetrazole, and the salts
thereof, particularly pharmaceutically acceptable salts thereof.

25 Compounds of the general formula I in which R₁, R₂ and R₃
differ from one another are chiral. It has been found that the
R-enantiomers of some of these classes or sub-classes of compounds (and
the S-enantiomers for other classes or subclasses) are useful as cellular

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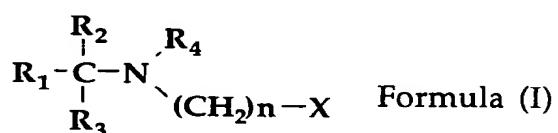
rescue agents for the treatment and prevention of diseases in which cell death occurs by apoptosis, such as in many neurodegenerative disorders. For a particular class or subclass of compounds the inactive enantiomer does not prevent apoptosis but can antagonize the antiapoptotic actions of 5 the active enantiomers, and are useful as research tools. The achiral compounds also display cellular rescue properties.

The present invention also relates to the use of compounds of general formula I, as defined above, and salts thereof, as cellular rescue agents for the treatment and prevention of diseases in which cell death 10 occurs by apoptosis including but not limited to, stroke, head trauma, Bell's palsy, spinal cord and other nerve crush injuries, Alzheimer's disease, Parkinson's disease, Pick's disease, amyotrophic lateral sclerosis, Huntington's disease, multiple sclerosis, cardiac myopathies, nephropathy, retinopathy, diabetic complications, glaucoma, as well as idiopathic 15 neuropathies. Accordingly, the present invention provides a method for treating a condition wherein cell death occurs by apoptosis comprising administering an effective amount of a compound of the formula I to an animal in need thereof.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

20 **Compounds of the Invention**

The present invention relates to compounds of the general formula I,



25 wherein:

R_1 is $(\text{CH}_2)_m\text{CH}_3$ where m is 0 or an integer in the range from 1 to 16, or an alkenyl, alkynyl, alkoxy, alkylthio, or alkyl sulfinyl group having from 2 to 17 carbon atoms. R_1 may be unsubstituted or substituted with at least one

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of the substituents selected from hydroxy, aldehyde, oxo, lower acyloxy, halogen, thio, sulfoxide, sulfone, phenyl, halogen-substituted phenyl, hydroxy-substituted phenyl, cycloalkyl having from 3 to 6 carbon atoms and heterocyclic substituents having between 3 and 6 atoms, of which

5 from 1 to 3 are heteroatoms selected from O, S and/or N,

$R_2 = H, CH_3$ or CH_2CH_3 ,

$R_3 = H$ or CH_3 ,

$R_4 = H$ or CH_3 ,

$R_5 =$ lower alkyl having from 1 to 5 carbon atoms,

10 n is an integer in the range from 1 to 3,

and X is carboxyl ($COOH$), carbalkoxy ($COOR_5$), cyano ($C\equiv N$), phosphonic acid (PO_3H_2), phosphonate ester ($PO_3[R_5]_2$) or 5-tetrazole, and the salts thereof.

In a preferred embodiment, the present invention provides a
15 compound of the Formula I (as described above) wherein

$R_1 = (CH_2)_mCH_3$ where m is 0 or an integer in the range from 1 to 16,

$R_2 = CH_3$,

$R_3 = H$,

$R_4 = H$ or CH_3 ,

20 $R_5 =$ lower alkyl having from 1 to 5 carbon atoms,

n is an integer in the range from 1 to 3,

and X is carboxyl ($COOH$) or carbalkoxy ($COOR_5$), cyano ($C\equiv N$), phosphonic acid (PO_3H_2), phosphonate ester ($PO_3[R_5]_2$) or 5-tetrazole, or a pharmaceutically acceptable salt thereof.

25 Preferred compounds of the invention include:

2-(2-Propylamino)acetic acid;

2-(1-Hexylamino)acetic acid;

(S)-2-(2-Heptylamino)acetic acid;

3-(2-Propylamino)propionic acid;

30 3-(1-Hexylamino)propionic acid;

(R)-3-(2-Heptylamino)propionic acid;

- 5 -

2-(2-Propylmethylamino)acetic acid;
2-(1-Hexylmethylamino)acetic acid;
(S)-2-(2-Heptylmethylamino)acetic acid;
3-(2-Propylmethylamino)propionic acid;
5 3-(1-Hexylmethylamino)propionic acid;
(R)-3-(2-Heptylmethylamino)propionic acid;
2-(2-Propylamino)acetonitrile;
(R)-2-(2-Pentylamino)acetonitrile;
2-(1-Hexylamino)acetonitrile;
10 (S)-2-(2-Heptylamino)acetonitrile;
(R)-3-(2-Heptylamino)propionitrile;
2-(2-Propylmethylamino)acetonitrile;
(R)-2-(2-Pentylmethylamino)acetonitrile;
2-(1-Hexylmethylamino)acetonitrile;
15 (S)-2-(2-Heptylmethylamino)acetonitrile;
(R)-3-(2-Heptylmethylamino)propionitrile;
2-(2-Propylamino)ethanephosphonic acid;
(R)-2-(2-Pentylamino)ethanephosphonic acid;
(S)-2-(2-Heptylamino)ethanephosphonic acid;
20 2-(2-Propylmethylamino)ethanephosphonic acid;
(S)-2-(2-Heptylmethylamino)ethanephosphonic acid; and
(R)-2-(2-Heptylamino)ethane-5-tetrazole.

Compounds of formula I which are optically pure enantiomers are novel. Achiral and racemic compounds are novel with 25 the exception of the following exclusions, although their properties as cellular rescue agents are not known.

a) for X = COOH; n = 1; R₃ = R₄ = H, exclude compounds for which:
R₂ = H and m = 1 to 4, 6, 7, 9, 11, or 13, and
R₂ = CH₃ and m = 0, 1 or 2.

30 b) for X = COOH; n = 1; R₃ = H; R₄ = CH₃, exclude compounds for which:
R₂ = H and m = 2 or 3, and

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$R_2 = CH_3$ and $m = 0$.

c) for $X = COOR_5$; $n = 1$; $R_3 = R_4 = H$, exclude compounds for which:
 $R_2 = H$ and $m = 1$ to 4, or 9, and
 $R_2 = CH_3$ and $m = 0$ or 1, and
5 $R_5 =$ methyl, ethyl, t-butyl.

d) for $X = COOH$; $n = 2$; $R_3 = R_4 = H$, exclude compounds for which:
 $R_2 = H$ and $m = 1$ to 4, 6, 9 or 11, and
 $R_2 = CH_3$ and $m = 0$, 1 or 4.

e) for $X = COOH$; $n = 2$; $R_3 = H$; $R_4 = CH_3$, exclude compounds for which:
10 $R_2 = H$ and $m = 1$ or 2.

f) for $X = COOR_5$; $n = 2$; $R_3 = R_4 = H$, exclude compounds for which:
 $R_2 = H$ and $m = 1$ to 5, 9 or 15,
 $R_2 = CH_3$ and $m = 0$ or 1, and
15 $R_5 =$ methyl, ethyl, t-butyl.

g) for $X = COOR_5$; $n = 2$; $R_3 = H$; $R_4 = CH_3$, exclude compounds for which:
 $R_2 = H$ and $m = 1$ or 2,
 $R_2 = CH_3$ and $m = 0$, and
20 $R_5 =$ methyl, ethyl, t-butyl.

h) for $X = COOH$; $n = 3$; $R_3 = R_4 = H$, exclude compounds for which:
25 $R_2 = H$ and $m = 2$ or 6.

i) for $X = COOR_5$; $n = 3$; $R_3 = R_4 = H$, exclude compounds for which:
 $R_2 = H$ and $m = 2$,
 $R_2 = CH_3$ and $m = 0$ or 1, and
30 $R_5 =$ methyl, ethyl, t-butyl.

j) for $X = C\equiv N$ (cyano); $n = 1$; $R_3 = R_4 = H$, exclude compounds for which:
 $R_2 = H$ and $m = 1$, 2, 4, 5 or 6, and
 $R_2 = CH_3$ and $m = 0$, 1 or 2.

k) for $X = C\equiv N$; $n = 1$; $R_3 = H$; $R_4 = CH_3$, exclude compounds for which:
 $R_2 = H$ and $m = 1$, and

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$R_2 = CH_3$ and $m = 0$.

1) for $X = C\equiv N$; $n = 2$; $R_3 = R_4 = H$, exclude compounds for which:

$R_2 = H$ and $m = 1, 2, 3, 4$ or 6 , and

$R_2 = CH_3$ and $m = 0, 1$ or 4 .

5 m) for $X = C\equiv N$; $n = 2$; $R_3 = H$; $R_4 = CH_3$, exclude compounds for which:

$R_2 = H$ and $m = 2$, and

$R_2 = CH_3$ and $m = 0$.

n) for $X = C\equiv N$; $n = 3$; $R_3 = R_4 = H$, exclude compounds for which:

$R_2 = H$ and $m = 1$ to 4 , and

$R_2 = CH_3$ and $m = 1$ or 2 .

10 o) for $X = PO_3H_2$; $n = 2$; $R_3 = R_4 = H$, exclude compounds for which:

$R_2 = CH_3$ and $m = 0, 1$ or 5 .

p) for $X = PO_3(R_5)_2$; $n = 2$; $R_3 = R_4 = H$, exclude compounds for which:

$R_2 = CH_3$ and $m = 0$ or 1 , and

$R_5 = ethyl$.

15 q) for $X = 5$ -tetrazole; $n = 2$; $R_3 = R_4 = H$, exclude compounds for which:

$R_2 = CH_3$ and $m = 0$.

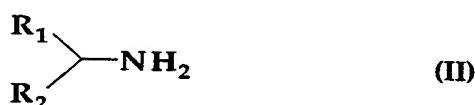
Particularly preferred are those of the R and S configurations, depending on the subclass of compound. Methods of resolving the 20 racemates are known. Suitable methods include fractional crystallization, derivatization of the racemate followed by stereospecific enzymatic removal of the attached group, and chromatography. It is preferred, however, to make chiral compounds of formula I from chiral reactants, using reactions that do not destroy the stereochemistry. When referring to enantiomers, it 25 is preferred that an enantiomer shall not contain more than 3% of the compound of the opposite configuration. It is particularly preferred that an enantiomer contain less than 1% of the corresponding enantiomer of the opposite configuration.

Some of the inactive enantiomers for a given class or subclass of compounds strongly antagonize the antiapoptotic actions of the active enantiomers, and are useful as research tools.

5 The invention extends to salts of compounds of formula I. For administration the salts should be pharmaceutically acceptable, but other salts may be useful, for example, in synthesis or for purification.

Methods of Preparing Compounds of the Invention

10 Compounds of the invention can be prepared in a variety of different ways. One process involves the addition of a primary amine of formula (II)



across the olefinic double bond of α,β -unsaturated carboxylic acid esters (such as methyl acrylate), of vinylphosphonic acids esters or of α,β -unsaturated nitriles (such as acrylonitrile) of formula (III)[21],

15



wherein X is a polarized group such as carboxylic ester, phosphonic ester or nitrile to give the corresponding N-alkylamino propionic esters, ethanephosphonic esters and propionitriles.

20 It is possible to use an amine of the formula (II) in which R_1 differs from R_2 in the form of a racemate and to separate the enantiomers subsequently, but it is preferred to use an amine in substantially enantiomerically pure form.

25 Chiral primary amines (R- or S- forms) were prepared by recrystallization of the tartrates of the racemates from methanol [22], except for (R) and (S)-2-butylamines which were purchased from Aldrich Chemical

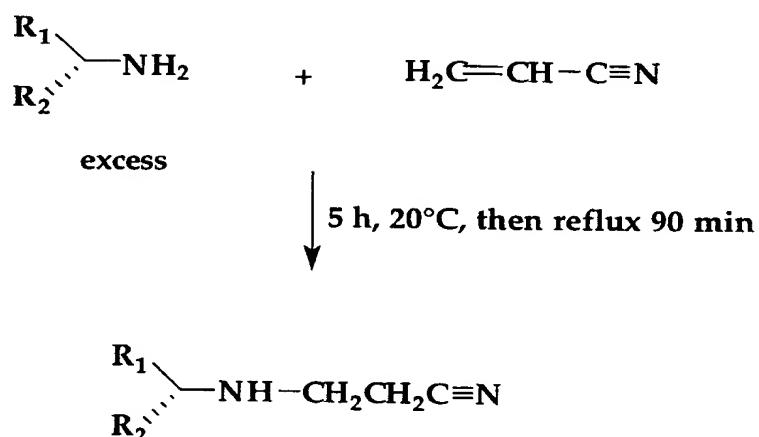
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Co. Enantiomeric purity was determined using gas chromatography with a chiral capillary column and chiral derivatizing agent [23]. In analogy to the above, chiral primary amines can also be added to the C-C double bond of methyl acrylate, diethyl vinylphosphonate or acrylonitrile to give the 5 corresponding chiral methyl N-alkylaminopropionate, chiral diethyl N-alkylaminoethanephosphonate or chiral N-alkylaminopropionitrile.

In one embodiment, an excess of a chiral amine adds to the olefinic bond of acrylonitrile, as depicted in the following scheme.

Excess Amine and Acrylonitrile:

10



where R_1 = hydrogen, methyl or ethyl and

R_2 = methyl, ethyl, propyl, butyl, pentyl, hexyl.

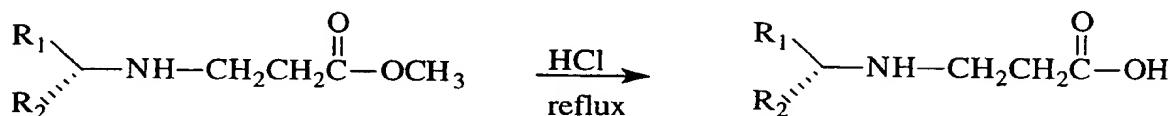
In another embodiment an excess of the amine can be added to the olefinic double bond of diethyl vinylphosphonate to give the 15 corresponding diethyl N-alkylaminoethanephosphonate. Hydrochloric acid hydrolysis of the aminophosphonic diester yields the corresponding aminophosphonic acid as the hydrochloride salt.

In yet another embodiment an excess of the amine can be added to the olefinic double bond of methyl acrylate to give the corresponding 20 methyl N-alkylaminopropionate [24]. Hydrolysis of the carboxylate ester

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with hydrochloric acid produces an amino acid as its hydrochloride salt, in accordance with the following reaction scheme:

Hydrolysis of Esters:



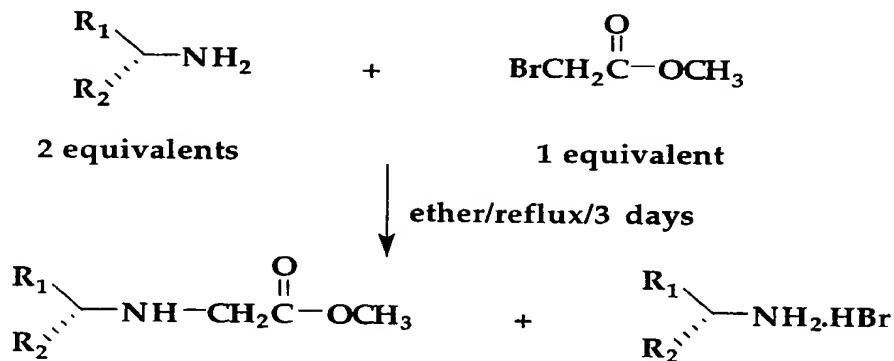
5 A second process to give compounds of the invention which contain only one carbon atom between the nitrogen atom and the functional group involves condensing a primary aliphatic amine of formula (II) with a bromomethyl reactant of formula (IV)



10 wherein L is a leaving group, for example a halide, tosyl or mesyl group (bromide is preferred), and X is carboalkoxy (carbomethoxy or carbethoxy is preferred), nitrile or phosphodiethoxy. Again, the amine can be used in racemic or enantiomerically pure form. In one preferred embodiment, two equivalents of the amine are reacted with one equivalent of the bromomethyl analogue of formula (IV) to form the required 15 aminomethanecarboxylate (glycine) ester and the hydrobromide salt of the amine, which can be isolated and reused, in accordance with the following reaction scheme.

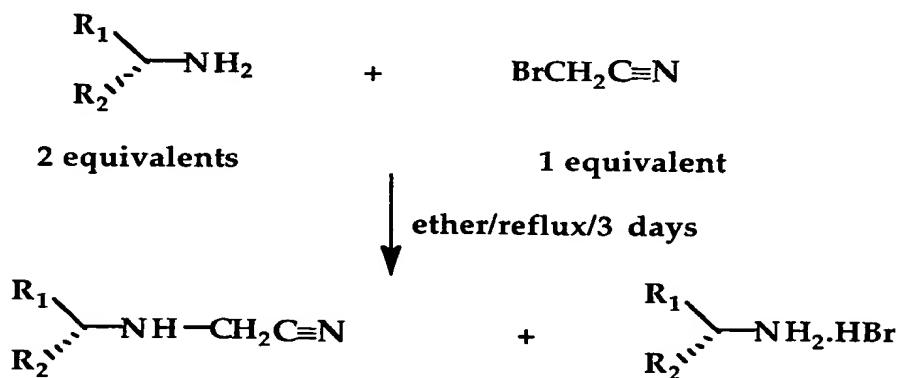
- 11 -

Two Equivalents of Amine and One Equivalent of Bromomethyl Ester in Ether:



In another preferred embodiment, two equivalents of the amine
 5 are reacted with one equivalent of the bromomethyl analogue of formula
 (IV) to form the required aminomethane nitrile (aminoacetonitrile) and the
 hydrobromide salt of the amine, which can also be isolated and reused, in
 accordance with the following reaction scheme.

Two Equivalents of Amine and One Equivalent of Bromoacetonitrile in
 10 Ether:



Another route to compounds of the invention involves trifluoroacetylation of the amine, followed by reaction with bromomethyl,

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bromoethyl or bromopropyl analogues of esters of carboxylic acids or nitriles of formula (V).



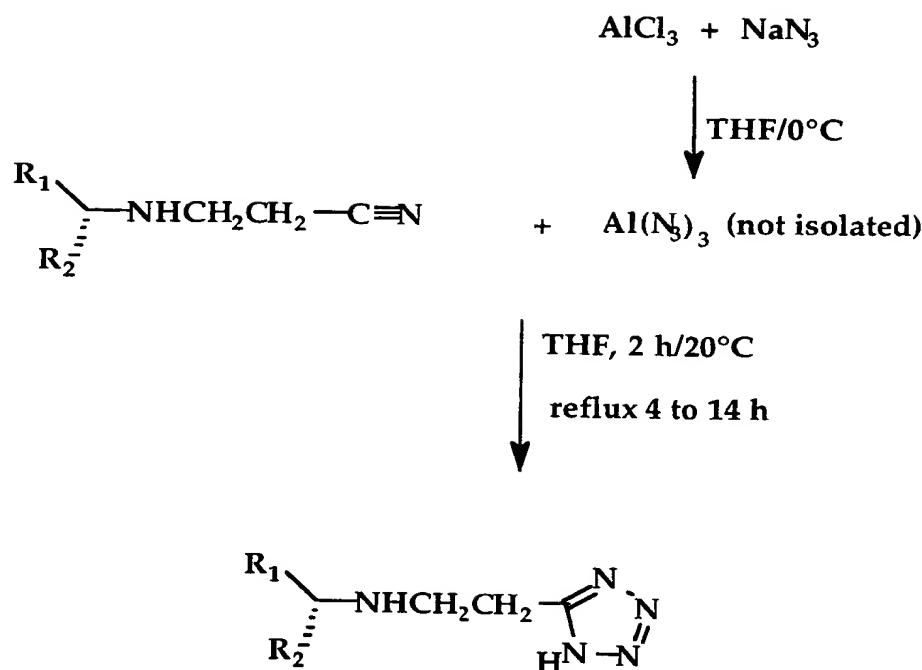
wherein L is a leaving group, for example a halide, tosyl or mesyl group (bromide is preferred), n is 1, 2 or 3 and X is carboalkoxy (methoxy or ethoxy is preferred), nitrile or phosphodethoxy.

The amine can be used in racemic or enantiomerically pure form. The amine is reacted with trifluoroacetic anhydride or a trifluoroacetyl halide in an inert organic solvent, for instance a chlorinated hydrocarbon such as methylene dichloride, chloroform or carbon tetrachloride, and a base, for example an organic base such as triethylamine. The N-trifluoroacetylamine is then refluxed with a bromo compound of formula (V), suitably in the presence of a base such as potassium t-butoxide in a polar solvent, for example acetonitrile, and in the presence of a crown ether catalyst, for example 18-crown-6. The product of this reaction is then hydrolyzed, suitably by reaction with a base such as an alkali metal hydroxide in an alcoholic solution.

Tetrazole compounds of the invention were prepared by the addition of azide ion to a nitrile triple bond [25]. Again, the amine can be used in racemic or enantiomerically pure form. In one preferred embodiment azide ion is generated by the slow addition of aluminum chloride to a solution/suspension of sodium azide in tetrahydrofuran at 0°C. To the resulting solution of aluminum azide is added the nitrile (prepared as in the pathways described above) in tetrahydrofuran at room temperature, followed by stirring for 2 hours and then gentle refluxing for several hours, according to the following scheme.

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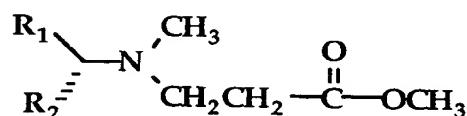
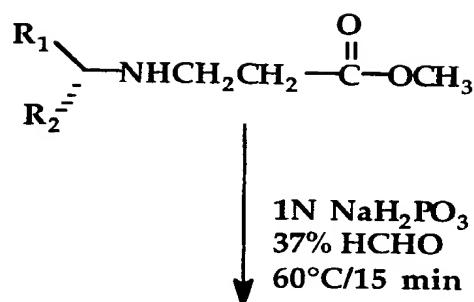
Addition of Azide Ion to Nitrile:



N-Methylation of the various secondary amines described above is achieved by reductive methylation using formaldehyde and sodium phosphite [26]. Again, the amine can be used in racemic or enantiomerically pure form. An amino carboxylate ester or amino nitrile (as the hydrochloride salt or free base) is dissolved in aqueous sodium dihydrogen phosphite and reacted with an excess of 37% aqueous formaldehyde at 60°C for 15 min. The product is isolated by ether extraction after basification of the ice-cold reaction mixture with sodium hydroxide. A preferred embodiment is shown in the following reaction scheme.

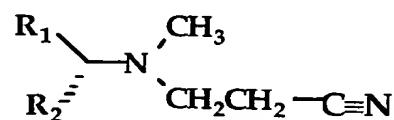
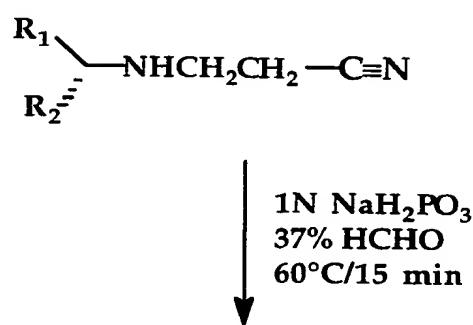
- 14 -

N-Methylation of an Amino Ester:



Yet another preferred embodiment is shown in the following reaction scheme.

5 N-Methylation of an Amino Nitrile:



Therapeutic Methods of the Invention

As hereinbefore mentioned, the compounds of the formula I (as described above) have many therapeutic applications.

5 In one aspect, the present invention provides a method for treating or preventing a condition wherein cell death occurs by apoptosis comprising administering an effective amount of a compound of the formula I to an animal in need thereof.

10 The term "effective amount" as used herein means an amount effective, at dosages and for periods of time necessary to achieve the desired result. The term "animal" as used herein includes all members of the animal kingdom including humans.

15 In another aspect, the present invention provides a use of a compound of the formula I to treat or prevent a condition wherein cell death occurs by apoptosis.

20 In yet a further aspect, the present invention provides a use of a compound of the formula I to prepare a medicament to treat or prevent a condition wherein cell death occurs by apoptosis.

25 Conditions wherein cell death occurs by apoptosis includes, but are not limited to, stroke, head trauma, Bell's palsy, spinal cord and other nerve crush injuries, Alzheimer's disease, Parkinson's disease, Pick's disease, amyotrophic lateral sclerosis, Huntington's disease, multiple sclerosis, cardiac myopathies, nephropathy, retinopathy, diabetic complications, glaucoma, as well as idiopathic neuropathies.

Pharmaceutical Compositions

30 The compounds of the general formula I may be formulated into pharmaceutical compositions for administration to subjects in a biologically compatible form suitable for administration *in vivo*. The compositions containing the compounds of the invention can be prepared by per se known methods for the preparation of pharmaceutically acceptable compositions which can be administered to subjects, such that an effective quantity of the active substance is combined in a mixture with a pharmaceutically acceptable vehicle. Suitable vehicles are described, for

- 16 -

example, in Remington's Pharmaceutical Sciences (Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., USA 1985). On this basis, the compositions include, albeit not exclusively, solutions of the substances in association with one or more pharmaceutically acceptable vehicles or diluents, and contained in buffered solutions with a suitable pH and iso-osmotic with the physiological fluids.

5 The active substance may be administered in a convenient manner such as by injection (subcutaneous, intravenous, etc.), oral administration, inhalation, transdermal application, or rectal 10 administration.

In oral administration, the compounds may be administered as tablets, coated tablets, gelatine capsules, capsules, cachets, and solutions or suspensions to be taken orally. The compounds can also be administered parenterally or through any other suitable administrative route such as 15 intravenous, subcutaneous, depot injections, intramuscular, intrathecal, intraventricular, intra-articular, rectal (suppository, enema), sublingual, buccal, intra-ocular, intra-vitreo, transdermal (skin patch), nasal drops (nebulizer, insufflation), liposomal delivery systems. The daily dosage could likely range from 1 to 100 mg.

20 Accordingly, in another aspect, the present invention provides a pharmaceutical composition comprising a compound of general formula (I) in admixture with a suitable diluent or carrier. The compound may be achiral or a substantially enantiomerically pure R- or S-enantiomer, or a 25 pharmaceutically acceptable salt thereof, in admixture with pharmaceutically acceptable diluents or carriers. The compositions are useful in the treatment or prevention of conditions in which cell death occurs by apoptosis.

In another aspect, the present invention provides a commercial 30 package containing as active ingredient a compound of the formula I, or a pharmaceutically acceptable salt thereof, together with instructions for its use for the treatment or prevention of a condition in which cell death occurs by apoptosis.

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EXAMPLES

Example 1:

In Vitro Protocol for Assessing the Antiapoptotic Capacity of Various Compounds in Cerebellar Granule Cells:

5 The following biological data demonstrate that the compounds of the invention exhibit antiapoptotic properties.

Cultures of cerebellar granule cells (CGC) can be induced into apoptosis by the addition of a high concentration of cytosine arabinoside (AraC) [27]. It has been shown that this is a p53 dependent apoptosis [28].

10 We have measured the antiapoptotic effect of some amino acids, amino esters, amino phosphonic acids, amino nitriles and amino tetrazoles using this system.

Cultures of CGC were obtained from 6-8 day old Wistar rat pups. Cultures were grown on glass in 35 mm petri dishes for three days and then 15 used for experiments. Aliquots (20 ul) of drug solutions (AraC, anti-apoptotic drugs, drug vehicles) were added to the medium of the culture. 24 Hours later the cultures were fixed with FAM, and stained with bis-benzamide. Normal and apoptotic nuclei were counted to a total of 90-120 cells per culture. The optimum concentration of AraC was found to 20 be 300 uM.

The results are summarized in Tables 1 - 4.

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Table 1 - Rescue by Amino Acids and Esters in the CGC Assay

	<u>Compound</u>	<u>10⁻⁶ M</u>	<u>10⁻⁹ M</u>	<u>10⁻¹² M</u>	<u>Rescue</u>
Glycines (aminoacetic acids)					
5	2-Propyl	R	X	X	yes
	1-Hexyl	X	R	X	yes
	R-2-Heptyl	X	X	X	no
	S-2-Heptyl	R	R	R	yes
B-Alanines (aminopropionic acids)					
10	2-Propyl	X	R	R	yes
	2-Propyl-N-methyl	R	R	X	yes
	R-2-Pentyl	X	X	X	no
	1-Hexyl	R	R	R	yes
	1-Hexyl-N-methyl	R	R	X	yes
	R-2-Heptyl		R	R	yes
15	R-2-Heptyl-N-methyl	R	R	R	yes
	S-2-Heptyl			X	no
B-Alaninates (esters)					
20	2-Propyl	X	X	X	no
	1-Hexyl	X	R	R	yes
	R-2-Heptyl-N-methyl	R	R	R	yes

R = rescue; X = no rescue

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Table 2 - Rescue by Amino Phosphonic Acids in the CGC Assay

<u>Compound</u>	<u>10⁻⁶ M</u>	<u>10⁻⁹ M</u>	<u>10⁻¹² M</u>	<u>Rescue</u>
2-Propyl	R	R	R	yes
R-2-Pentyl	R	X	X	yes
5 1-Hexyl	X	X	X	no
R-2-Heptyl	R *	X	X	yes*
S-2-Heptyl	X	R	R	yes

* The presence of 0.5% S-enantiomer (which is potent at 10⁻¹² M) in the R-enantiomer is probably responsible for the apparent rescue by the 10 R-enantiomer at 10⁻⁶ M.

Table 3 - Rescue by Amino Tetrazoles in the CGC Assay

<u>Compound</u>	<u>10⁻⁶ M</u>	<u>10⁻⁹ M</u>	<u>10⁻¹² M</u>	<u>Rescue</u>
R-2-Heptyl	R	R	R	yes
S-2-Heptyl	X	X	X	no

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Table 4 - Rescue by Amino Nitriles in the CGC Assay

<u>Compound</u>	<u>10⁻⁶ M</u>	<u>10⁻⁹ M</u>	<u>10⁻¹² M</u>	<u>Rescue</u>	
Acetonitriles					
5	2-Propyl	R	R	R	
	R-2-Pentyl	X	R	X	
	S-2-Pentyl	X	X	X	
	1-Hexyl	X	R	R	
	R-2-heptyl	X	X	X	
	S-2-Heptyl	X	R	R	
10	Propionitriles				
	2-Propyl	X	X	X	
	2-Propyl-N-methyl	T	T	X	
	R-2-Pentyl	X	X	X	
	tert-Amyl	X	X	X	
	tert-Amyl-N-methyl	X	X	X	
	3-Pentyl	R	R	X	
	1-Hexyl	X	X	X	
	1-Hexyl-N-methyl	X	X	X	
	R-2-Heptyl	X	R	R	
20	R-2-Heptyl-N-				
	methyl	X	R	X	
	S-2-heptyl	X	X	X	

R = rescue; X = no rescue; T = toxic

25 **Detailed Synthetic Procedures**

The following non-limiting examples of synthetic procedures are provided.

Example 2:

Methyl 3-(1-hexylamino)propionate hydrochloride [Methyl 30 N-(1-hexyl)-β-alaninate]

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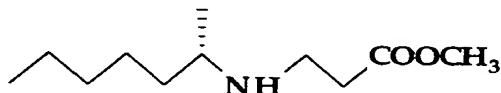
To ice-water-cooled 1-hexylamine (7.58 g, 75 mmol) was added dropwise methyl acrylate (4.3 g, 50 mmol). After completion of the addition the temperature was allowed to rise to room temperature and the reaction 5 solution was stirred for 5 hours, then refluxed for 90 minutes. After stirring overnight at 20°C the product, methyl 3-(1-hexylamino)propionate, was distilled (b.p. = 85-88°C/2 mm; lit. b.p. 80-84°C/0.5 mm) as a clear, colorless liquid in a yield of 55%. The hydrochloride salt was prepared by the addition of methanolic HCl (15%) to an ethereal solution of the free base; 10 m.p. = 204-205°C (lit. m.p. 190-192°C).

Mass spectrum: m/e: 187 (M+); 116 (M-C₅H₁₁); 84.

Example 3:

(R)-Methyl 3-(2-heptylamino)propionate hydrochloride [(R)-Methyl N-(2-heptyl)-β-alaninate]

15



Prepared according to Example 2. The hydrochloride salt was recrystallized from methanol/ether; m.p. = 89.5-90.5°C.

Mass spectrum: m/e: 201 (M+); 186 (M-CH₃); 130 (M-C₅H₁₁)

Example 4:

20 Methyl 3-(2-propylamino)propionate hydrochloride [Methyl N-(2-propyl)-β-alaninate]

Prepared according to Example 2. The hydrochloride salt was crystallized from methanol/ether; m.p. = 108-110°C (lit. m.p. 107°C).

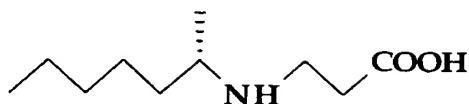
Mass spectrum: m/e: 145 (M+); 130 (M-CH₃); 98; 72; 56.

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Example 5:

(R)-3-(2-Heptyl amino)propionic acid hydrochloride
[(R)-N-(2-heptyl)-β-alanine]

5



(R)-3-(2-Heptyl amino)propionitrile (7.5 g, 44.6 mmol) (prepared according to Example 18) was refluxed with concentrated hydrochloric acid (50 mL) for 4 h. After filtration of insoluble ammonium chloride, the aqueous solution was rotary evaporated to dryness. The residue was stirred 10 with dichloromethane (120 mL) for 2 hours and the insoluble ammonium chloride was filtered. The filtrate was concentrated, filtered again and then evaporated to give a colorless oil which crystallized on cooling. The yield of white hygroscopic product was quantitative; m.p. = 57-58°C.

Mass spectrum: m/e: 187 (M+); 172 (M-CH₃); 116 (M-C₅H₁₁); 72.
15 ¹H-NMR (D₂O, 300 MHz): 0.72 (t, 3H); 1.18 (d, 3H); 1.1-1.3 (m, 6H); 1.42/1.60 (2m, 1H each); 2.67 (t, 2H); 3.17 (m, 3H; αCH & CH₂COOH).

The title compound can also be prepared by hydrochloric acid hydrolysis of the methyl ester (prepared according to Example 3).

Example 6:

20 (S)-3-(2-Heptyl amino)propionic acid hydrochloride
[(S)-N-(2-heptyl)-β-alanine]

Prepared according to Example 5. The hydrochloride salt, m.p. = 56-58°C, is hygroscopic.

Mass spectrum: m/e: 187 (M+); 172 (M-CH₃); 128 (M-CH₂COOH); 116 (M-C₅H₁₁).
25

¹H-NMR (D₂O, 300 MHz): 0.75 (t, 3H); 1.18 (d, 3H); 1.1-1.3 (m, 6H); 1.45/1.60 (2m, 1H each); 2.68 (t, 2H); 3.20 (m, 3H; αCH & CH₂COOH).

Example 7:

3-(1-Hexylamino)propionic acid [N-(1-hexyl)- β -alanine]

Methyl 3-(1-hexylamino)propionate hydrochloride (see Example 2 for preparation) was hydrolyzed by refluxing in 2N HCl for 24 hours followed by evaporation to dryness; m.p. = 95-97°C (no lit. value).

Mass spectrum: m/e: 173 (M+); 102 (M-C₅H₁₁); 84; 72.

¹H-NMR (D₂O, 300 MHz): 0.73 (t, 3H); 1.17 (m, 6H); 1.52 (m, 2H); 2.68 (t, 2H); 2.93 (t, 2H); 3.18 (t, 2H).

Example 8:

10 3-(2-Propylamino)propionic acid hydrochloride [N-(2-propyl)- β -alanine]

Prepared by hydrolysis of the ester (Example 7). The product is a white powder, m.p. = 154-155°C (no lit. value).

Mass spectrum: m/e: 131 (M+); 116 (M-CH₃); 98; 56.

¹H-NMR (D₂O, 300 MHz): 1.20 (d, 6H); 2.70 (t, 2H); 3.19 (t, 2H); 3.32 (m, 1H).

Example 9:

15 Ethyl 2-(2-propylamino)acetate hydrochloride [Ethyl N-(2-propyl)glycinate]



20 To a solution of 2-propylamine (4.4 g, 75 mmol) in ether (100 mL) was added ethyl bromoacetate (6.26g, 37.5 mmol). The solution was stirred at 20°C for 3 days. The precipitated 2-propylamine hydrobromide was filtered and the filtrate rotary evaporated to give 5.4 g a clear pale yellow liquid (crude yield = 99%). The hydrochloride salt was prepared and recrystallized from ethanol/ether; m.p. = 120-121°C (no lit. value).

25 Mass spectrum: m/e: 145 (M+); 130 (M-CH₃); 72 (M-COOC₂H₅).

Example 10:

2-(2-Propylamino)acetic acid hydrochloride [N-(2-Propyl)glycine]

The sample was prepared from the nitrile (prepared according to Example 25) in 72% yield using a hydrolysis procedure similar to that

- 24 -

described in Example 12. The hydrochloride salt was recrystallized from acetone; m.p. = 180-184°C (lit. m.p. 203-204.5°C; 182-183°C).

Mass spectrum: (CI). 118 (M+1); 102 (M-CH₃); 72 (M-CO₂H); (EI). 117 (M+); 102 (M-CH₃); 72 (M-COOH).

5 1H-NMR (D₂O, 300 MHz): 1.19 (d, 6H); 3.33 (m, 1H); 3.79 (s, 2H).

Example 11:

2-(1-Hexylamino)acetic acid hydrochloride [N-(1-Hexyl)glycine] 1HxActAc

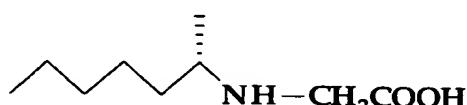
The sample was prepared from the nitrile (procedure analogous to that described in Example 10) in 72% yield using a hydrolysis procedure 10 similar to that described in Example 12. The hydrochloride salt was recrystallized from acetone; m.p.= 162-164°C (lit. m.p. 215-218°C).

Mass spectrum: m/e: 159 (M+); 114 (M-CO₂H); 88 (M-C₅H₁₁).

1H-NMR (D₂O, 300 MHz): 0.72 (t, 3H); 1.20 (m, 6H); 1.55 (m, 2H); 2.96 (t, 2H); 3.77 (s, 2H).

15 **Example 12:**

(R)-2-(2-Heptylamino)acetic acid hydrochloride [(R)-N-(2-Heptyl)glycine]



A solution of (R)-2-(2-heptylamino)acetonitrile (1.20 g, 7.79 mmol) (prepared according to Example 23) in concentrated HCl (12 mL) and 20 water (5 mL) was heated for 48 hours at 90°C. After cooling to room temperature, the reaction mixture was concentrated to dryness, filtered, and washed with ethanol to remove NH₄Cl. The resulting filtrate was concentrated to give a crude product (1.40 g). A solution of the crude product (0.60 g) in concentrated HCl (20 mL) and water (10 mL) was heated 25 for 24 hours at 90°C. After cooling to room temperature, the reaction mixture was taken to dryness and triturated in ether to give the hydrochloride salt as a crystalline solid (0.60 g, overall 37% yield); m.p.= 162-164°C.

- 25 -

Mass spectrum: m/e: (CI). 174 (M+1); 158 (M-CH₃); 102 (M-C₅H₁₁).

1H-NMR (D₂O, 300 MHz): 0.74 (t, 3H); 1.18 (d, 3H); 1.1-1.3 (m, 6H); 1.45/1.60 (2m, 1H each); 3.21 (m, 1H); 3.79 (s, 2H).

Example 13:

5 (S)-2-(2-Heptylamino)acetic acid hydrochloride [(S)-N-(2-Heptyl)glycine]

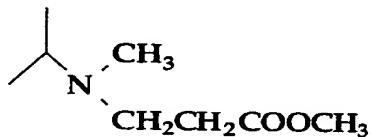
The product was prepared as described in Example 12 in 72% overall yield by hydrolysis of the nitrile hydrochloride salt; m.p.= 161-163°C.

Mass spectrum: m/e: (CI). 174 (M+1); 156 (M-OH); 128 (M-CO₂H).

1H-NMR (D₂O, 300 MHz): 0.73 (t, 3H); 1.18 (d, 3H); 1.47, 1.60 (2m, 1H each); 3.21 (m, 1H); 3.78 (s, 2H).

Example 14:

Methyl 3-(2-propylmethylamino)propionate hydrochloride [Methyl N-(2-propyl)-N-methyl-β-alaninate]



15 To a solution of methyl 3-(2-propylamino)propionate hydrochloride (Example 10)(0.907 g; 5 mmol) in 1N sodium dihydrogen phosphite (25 mL) was added 37% formaldehyde (2.1 mL, 23 mmol). The solution was stirred at 60°C for 10 min, then cooled in an ice-water bath and basified with 10% sodium hydroxide (10 mL). The resulting solution was saturated with sodium chloride (9 g) and immediately extracted with ether (3 x 15 mL). The combined filtrates were dried over anhydrous magnesium sulfate and evaporated to dryness to give a clear colorless liquid. The hydrochloride salt, prepared by the addition of methanolic HCl to an ether solution of the free base, precipitated as a viscous oil in 83 % yield.

20

25 Mass spectrum: m/e: 159 (M+); 144 (M-CH₃); 86 (M-CH₂COOCH₃).

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Example 15:

(R)-Methyl 3-(2-heptylmethylamino)propionate hydrochloride [(R)-Methyl N-(2-heptyl)-N-methyl- β -alaninate]

The hydrochloride salt was obtained in 93% yield as a colorless viscous liquid.

Mass spectrum: m/e: 215 ((M+); 200 (M-CH₃); 144 (M-C₅H₁₁).

Example 16:

(R)-3-(2-Heptylmethylamino)propionic acid hydrochloride [N-(2-Heptyl)-N-methyl- β -alanine]

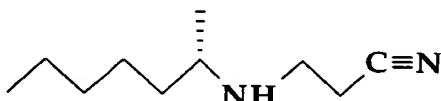
The hydrochloride salt precipitated as a colorless, viscous oil.

Mass spectrum: m/e: 201 (M+); 186 (M-CH₃); 130 (M-C₅H₁₁).

¹H-NMR (D₂O, 300 MHz): 0.72 (t, 3H); 1.18 (m, 9H); 1.47, 1.59 (2m, 1H each); 2.65 (d, 3H); 2.74 (t, 2H); 3.11 (m, 1H); 3.34 (m, 2H).

Example 17:

(R)-3-(2-Heptylamino)propionitrile hydrochloride



To ice-water-cooled (R)-2-heptylamine (99.4% R)(9.28 g, 80.7 mmol) was added dropwise acrylonitrile (2.85 g, 3.543 mL, 54 mmol). After completion of the addition the temperature was allowed to rise to room temperature and the reaction solution was stirred for 5 hours, then refluxed for 90 minutes. After stirring overnight at 20°C the product, (R)-3-(2-heptylamino)propionitrile, was distilled as a clear, colorless liquid, b.p. = 101-102°C/2 mm, with a yield of 85%. The hydrochloride salt was prepared by the addition of ethanolic HCl (15%) to an ethereal solution of the free base; m.p. = 134-135°C.

Mass spectrum: m/e: (CI) 169 (M+H)+; 153 (M-CH₃); 97 (M-C₅H₁₁).

¹H-NMR (D₂O, 300 MHz): 0.73 (t, 3H); 1.20 (d, m; 9 H); 1.45, 1.61 (2m, 1H each); 2.85 (t, 2H); 3.3 (m, 3H).

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Elemental Analysis: Calculated: %C = 58.66; %H = 10.34; %N = 13.68.

Found: %C = 58.73; %H = 10.53; %N = 13.47.

The starting material, (R)-2-heptylamine, was resolved from the racemate by repeated recrystallizations of its L-tartrate salt from methanol.

5 Eight recrystallizations using a ratio of volume (of methanol) to weight (of tartrate salt) of 2.4 to 2.6 (increasing as optical purity increased) gave the R-enantiomer with an optical purity of 99.4% R. The optical purity was assessed by derivatization with freshly prepared chiral reagent (S)-N-trifluoroacetylprolyl chloride and then gas chromatography on a 10 chiral column [23].

Example 18:

(S)-3-(2-Heptylaminoo)propionitrile hydrochloride

15 (S)-2-Heptylamine as its D-tartrate salt was prepared by recrystallization of the racemate (S-enriched, isolated and prepared from the combined filtrates of the R-enantiomer L-tartrate recrystallizations described in Example 17). The optical purity was 99.4% S. S-2HECN was prepared in 85% yield (b.p. 99-100°C/2 mm) as described for the R-enantiomer in Example 17. The hydrochloride salt was recrystallized from methanol/ether; m.p. = 133-134°C.

20 Mass spectrum: m/e: (CI) 169 (M+H)+; 153 (M-CH₃); 128 (M-CH₂CN); 97 (M-C₅H₁₁).

1H-NMR (D₂O, 300 MHz): 0.72 (t, 3H); 1.20 (d, m; 9H); 1.45, 1.62 (2m, 1H each); 2.85 (t, 2H); 3.29 (m, 3H).

Elemental Analysis: Calculated: %C = 58.66; %H = 10.34; %N = 13.68.

25 Found: %C = 58.61; %H = 10.10; %N = 13.42.

Example 19:

3-(2-Propylaminoo)propionitrile hydrochloride

30 The free base, b.p. = 94°C/30 mm (lit. b.p. 86-87°C/17 mm), was prepared according to the procedure in Example 17 and then converted to the hydrochloride salt which was recrystallized from methanol/ether; m.p. = 145.5-146°C (no lit. value).

Mass spectrum: m/e: 140 (M+); 97 (M-CH₃); 72 (M-CH₂CN).

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1H-NMR (D₂O, 300 MHz): 1.20 (d, 6H); 2.85 (t, 2H); 3.29 (t, 2H); 3.36 (m, 1H).

Example 20:

3-(1-Hexylamino)propionitrile hydrochloride

The hydrochloride salt was recrystallized from ethanol/ether;

5 m.p. = 188-189°C (no lit. value).

Mass spectrum: m/e: 154 (M+); 114 (M-CH₂CN); 83 (M-C₅H₁₁).

1H-NMR (D₂O, 300 MHz): 0.72 (t, 3H); 1.18 (m, 6H); 1.53 (m, 2H); 2.87 (t, 2H); 2.96 (t, 2H); 3.29 (t, 2H).

Example 21:

10 3-(3-Pentylamino)propionitrile hydrochloride

The free base, b.p. = 84-85°C/2 mm (no lit. value), was converted to the hydrochloride salt, m.p. = 118.5-119.5°C (no lit. value).

Mass spectrum: m/e: 140 (M+); 111 (M-C₂H₅); 100 (M-CH₂CN); 82; 70.

15 1H-NMR (D₂O, 300 MHz): 0.83 (t, 6H); 1.64 (m, 4H); 2.89 (t, 2H); 3.10 (m, 1H); 3.33 (t, 2H).

Example 22:

3-(t-Amylaminio)propionitrile hydrochloride

The free base, b.p. = 62-63°C/2 mm (no lit. value), was converted to the hydrochloride salt, m.p. = 199-200°C (no lit. value).

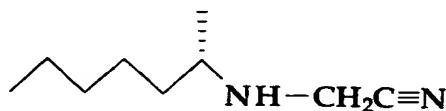
20 Mass spectrum: m/e: 140 (M+, absent); 125 (M-CH₃); 111 (M-CH₂CH₃)

1H-NMR (D₂O, 300 MHz): 0.82 (t, 3H); 1.20 (s, 6H); 1.58 (q, 2H); 2.83 (t, 2H); 3.29 (t, 2H).

Example 23:

(R)-2-(2-Heptylaminio)acetonitrile hydrochloride

25



To a solution of (R)-2-heptylamine (1.90 g, 16.5 mmol) in ether (25 mL) were added anhydrous Na₂CO₃ (1.60 g, 14.9 mmol), and bromoacetonitrile (0.92 mL, 13.2 mmol). The reaction mixture was stirred at

- 29 -

room temperature for 24 hours, and for another 14 hours at 80°C. After cooling to room temperature, the reaction mixture was filtered and the filtrate washed with HCl (3 N, 3x10 mL). The aqueous layer was basified with NaOH (6 N) and extracted with ether (3x25 mL). The resulting ethereal solution was dried over Na₂SO₄, and evaporated to dryness. The residue was fractionated by flash column chromatography (25% EtOAc/hexane, ether) to give a colorless oil (2.10 g, 82%). The hydrochloride salt was prepared by the addition of ethanolic HCl (15%) to an ethereal solution of the free base; m.p. = 152-3°C.

10 Mass spectrum: m/e: (CI).155 (M+1); 128 (M-CN); (EI) 139 (M-CH₃); 83 (M-C₅H₁₁).
1H-NMR (D₂O, 300 MHz): 0.75 (t, 3H); 1.20 (d, 3H); 1.15-1.35 (m, 6H); 1.47/1.62 (2m, 1H each); 3.35 (m, 1H); 4.18 (s, 2H).

Elemental Analysis: Calculated: %C = 56.68; %H = 10.04; %N = 14.69.

15 Found: %C = 56.81; %H = 10.20; %N = 14.46.

Example 24:

(S)-2-(2-Heptylamino)acetonitrile hydrochloride

20 The sample was prepared in 96% yield using the above-described procedure (Example 23). The hydrochloride salt was prepared by the addition of ethanolic HCl (15%) to an ethereal solution of the free base and was recrystallized from ethanol/ether. The salt sublimes during melting; m.p. = 140°C.

25 Mass spectrum: m/e: 154 (M+);139 (M-CH₃).
1H-NMR (D₂O, 300 MHz): 0.73 (t, 3H); 1.18 (d, m; 9 H); 1.43, 1.59 (2m, 1H each); 3.31 (m, 1H); 4.15 (s, 2H).

Elemental Analysis: Calculated: %C = 56.68; %H = 10.04; %N = 14.69.

Found: %C = 56.51; %H = 9.71; %N = 14.79.

Example 25:

2-(2-Propylamino)acetonitrile hydrochloride

30 The hydrochloride salt was recrystallized from methanol/ether; m.p. = 166-167°C (lit. m.p. 154-156°).

Mass spectrum: m/e: 98 (M+); 83 (M-CH₃); 56.

- 30 -

1H-NMR (D₂O, 300 MHz): 1.19 (d, 6H); 3.45 (m, 1H); 4.17 (s, 2H).

Example 26:

2-(1-Hexylamino)acetonitrile hydrochloride

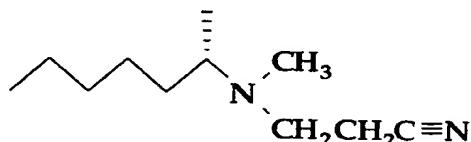
The free base of the sample was prepared in 62% yield using the above-described procedure (Example 23). The hydrochloride salt was prepared by the addition of ethanolic HCl (15%) to an ethereal solution of the free base, and was recrystallized from ethanol/ether; m.p.= 114-115°C (lit. m.p. 84-86°C).

Mass spectrum: m/e: (CI).141 (M+1)+; 126 (M-CN).

1H-NMR (D₂O, 300 MHz): 0.74 (t, 3H); 1.21 (m, 6H); 1.58 (m, 2H); 3.08 (t, 2H); 4.17 (s, 2H).

Example 27:

(R)-3-(2-Heptylmethylamino)propionitrile hydrochloride



(R)-3-(2-Heptylmethylamino)propionitrile (Example 17) (0.85 g, 5.0 mmol) was dissolved in 1N sodium dihydrogen phosphite (NaH₂PO₃)(25 mL) and 37% formaldehyde (2.1 mL, 23 mmol) was added. Sufficient dioxan was added to give a clear solution (10 mL). The solution was stirred at 60°C for 15 min during which time it became cloudy. To the cooled solution was then added 20% sodium hydroxide (20 mL) and sodium chloride (9 g). The basic solution was extracted with ether (3 x 15 mL). The combined extracts were dried over anhydrous magnesium sulfate and then evaporated to give a clear, colorless liquid in quantitative yield. The hydrochloride salt was prepared by adding methanolic HCl to an ether solution of the free base; m.p. = 98-98.5°C. Overall yield was 85%.

Mass spectrum: m/e: 182 (M+); 167 (M-CH₃); 142 (M-CH₂CN); 111 (M-C₅H₁₁).

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1H-NMR (D₂O, 300 MHz): 0.77 (t, 3H); 1.20 (d, 3H); 1.15-1.35 (m, 6H); 1.50/1.62 (2m, 1H each); 2.73 (s, 3H); 2.95 (t, 2H); 3.40 (m, 3H; aCH & CH₂CN).

Elemental Analysis: Calculated: %C = 60.39; %H = 10.60; %N = 12.80.

Found: %C = 59.55; %H = 10.29; %N = 13.67.

5 **Example 28:**

3-(2-Propylmethylamino)propionitrile hydrochloride

The hydrochloride salt was obtained in 90% yield; m.p. = 121-121.5°C (no lit. value)(see Example 27).

Mass spectrum: m/e: 126 (M+); 111 (M-CH₃); 86 (M-CH₂CN).

10 1H-NMR (D₂O, 300 MHz): 1.23 (d, 6H); 2.73 (s, 3H); 2.97 (t, 2H); 3.52 (br s, 2H); 3.60 (m, 1H).

Example 29:

3-(t-Amylmethylamino)propionitrile hydrochloride

The hydrochloride salt was obtained in 87% yield; m.p. = 137-138°C (no lit. value)(see Example 27).

Mass spectrum: m/e: 154 (M+); 139 (M-CH₃); 125 (M-C₂H₅); 72.

1H-NMR (D₂O, 300 MHz): 0.87 (t, 3H); 1.25 (6H); 1.67 (q, 2H); 2.10 (s, 2H); 2.73 (s, 3H); 2.94 (broad t, 2H).

Elemental Analysis: Calculated: %C = 56.68; %H = 10.04; %N = 14.69.

20 Found: %C = 56.62; %H = 10.12; %N = 14.62.

Example 30:

3-(1-Hexylmethylamino)propionitrile hydrochloride

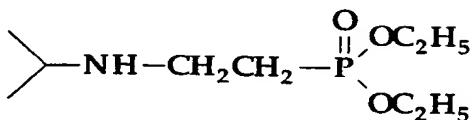
The hygroscopic hydrochloride salt was obtained in 75% yield; m.p. = 77-78.5°C (no lit. value)(see Example 27).

25 Mass spectrum: m/e: 168 (M+); 128 (M-CH₂CN); 97 (M-C₅H₁₁).

1H-NMR (D₂O, 300 MHz): 0.72 (t, 3H); 1.20 (m, 6H); 1.60 (m, 2H); 2.79 (s, 3H); 2.95 (t, 2H); 3.09 (t, 2H); 3.42 (t, 2H).

Example 31:

Diethyl 2-(2-propylamino)ethanephosphonate hydrochloride



To ice-cooled 2-propylamine (0.53 mL, 6.2 mmol) was added 5 dropwise diethyl vinylphosphonate (0.4 mL, 3.1 mmol) under N₂. The reaction mixture was stirred for 2 hours at 0°C, for 14 hours at room temperature, and for 10 hours at 100°C. After cooling to room temperature, the reaction mixture was concentrated to give a colorless oil (0.89 g). To a solution of the crude product (0.89 g) in ether (40 mL) was added ethanolic 10 HCl (15%), and then stirred for 2 hours at room temperature. The resulting crystallized hydrochloride salt was filtered, washed with ether to give a white solid (0.76 g, overall 95%); m.p. = 96-97°C (no lit. value).

Mass spectrum: m/e: 208 (M-CH₃)+; 180 (M-C₃H₇)+.

Example 32:

15 2-(2-Propylamino)ethanephosphonic acid hydrochloride

The hydrochloride salt of the product (starting from the diester, Example 31) was prepared in 32% overall yield using the procedure described in Example 37; m.p.= 164-166°C (no lit. value).

Mass spectrum: m/e: (Cl). 168 (M+1)+.

20 1H-NMR (D₂O, 300 MHz): 1.16 (d, 6H); 1.84 (m, 2H); 3.08 (q, 2H); 3.27 (m, 1H).

Example 33:

Diethyl 2-(1-hexylamino)ethanephosphonate hydrochloride

The crude product was prepared in 100% yield using the above-described procedure. The hydrochloride salt of the product was 25 prepared by the addition of ethanolic HCl (15%) to an ethereal solution of the product; the salt is a viscous oil.

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Mass spectrum: m/e: 265 (M)+, 194 (M-C₅H₁₁)+.

Example 34:

2-(1-Hexylamino)ethanephosphonic acid hydrochloride

5 The hydrochloride salt was prepared by hydrolysis of the diethyl ester using the method described in Example 37; m.p. = 145-150°C (no lit. value).

Mass spectrum: m/e: too involatile

1H-NMR (D₂O, 300 MHz): 0.70 (t, 3H); 1.15 (m, 6H); 1.50 (m, 2H); 1.90 (m, 2H); 2.88 (t, 2H); 3.08 (q, 2H).

10 Elemental Analysis: Calculated: %C = 39.11; %H = 8.62; %N = 5.70.

Found: %C = 39.34; %H = 8.53; %N = 5.89.

Example 35:

(R)-Diethyl 2-(2-heptylamino)ethanephosphonate hydrochloride

15 The free base was prepared in 93% yield using the above-described procedure. The hydrochloride salt was prepared by the addition of ethanolic HCl (15%) to an ethereal solution of the product; the salt is a viscous oil.

Mass spectrum: m/e: (CI). 280 (M+1)+; 264.(M-CH₃)+; 208 (M-C₅H₁₁)+.

Example 36:

20 (S)-Diethyl 2-(2-heptylamino)ethanephosphonate hydrochloride

The free base was prepared in 91% yield using the above-described procedure. The hydrochloride salt was prepared by the addition of ethanolic HCl (15%) to an ethereal solution of the product; the salt is a viscous oil.

25 Mass spectrum: m/e: (CI). 280 (M+1)+; 208 (M-C₅H₁₁)+.

Example 37:

(R)-2-(2-Heptylamino)ethanephosphonic acid hydrochloride

30 A solution of (R)-diethyl 2-(2-heptylamino)ethanephosphonate hydrochloride (0.19 g, 0.68 mmol) in concentrated HCl (7 mL) was heated at 90°C for 48 hours. The reaction mixture was then evaporated to dryness and the residue triturated with acetone. The white solid was filtered and air-dried-giving an 86% overall yield; m.p. = 106-112°C (no lit. value).

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Mass spectrum: m/e: too involatile

¹H-NMR (D₂O, 300 MHz): 0.73 (t, 3H); 1.25-1.10 (m, 12H); 1.43 (m, 1H); 1.58 (m, 1H); 1.89-1.78 (m, 2H); 3.22-3.05 (m, 3H).

5 Elemental Analysis: Calculated: %C = 41.62; %H = 8.93; %N = 5.39.
Found: %C = 41.68; %H = 9.10; %N = 5.23.

Example 38:

(S)-2-(2-Heptylaminoo)ethanephosphonic acid hydrochloride

The hydrochloride salt was prepared in 71% overall yield using
10 the above described procedure; m.p. = 106-113°C (no lit. value).

Mass spectrum: m/e: too involatile

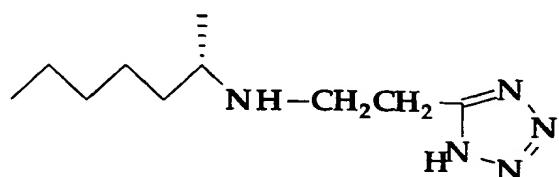
¹H-NMR (D₂O, 300 MHz): 0.73 (t, 3H); 1.25-1.10 (m, 12H); 1.44 (m, 1H); 1.59 (m, 1H); 1.89-1.78 (m, 2H); 3.22-3.05 (m, 3H).

Elemental Analysis: Calculated: %C = 41.62; %H = 8.93; %N = 5.39.

15 Found: %C = 41.43; %H = 9.09; %N = 5.33.

Example 39:

(R)-2-(2-Heptylaminoo)ethane-5-tetrazole hydrochloride



The compound as its hydrochloride salt was prepared in 28%
20 overall yield using the procedure described below in Example 40; the salt is a
viscous oil.

Mass spectrum: m/e: (Cl). 140 (M-C₅H₁₁)+; 128 (M-C₂H₃N₄)+.

¹H-NMR (D₂O, 300 MHz): 0.71 (t, 3H); 1.18 (m, 9H); 1.44, 1.60 (2m, 1H each);
3.30 (t+m; 3H); 3.45 (m, 2H).

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Example 40:

(S)-2-(2-Heptylamino)ethane-5-tetrazole hydrochloride

To an ice-cooled suspension of NaN_3 (2.60 g, 40 mmol) in dry THF (20 mL) was added AlCl_3 (1.36 g, 10 mmol) in portions under N_2 , and 5 stirred for 30 minutes. To the resulting suspension was added a solution of (S)-3-(2-heptylamino)propionitrile (1.68 g, 10 mmol) in THF (10 mL), and stirred for 2 hours at 0°C, then gently refluxed for 24 hours. After cooling to room temperature, the reaction mixture was quenched by the careful addition of HCl (3 N, 15 mL), water (5 mL), and the two layers were 10 separated. The lower aqueous layer was extracted with ethyl acetate (3x15 mL). The upper (organic) layer and the organic extracts were combined and dried over Na_2SO_4 , then taken to dryness to give crude product (oil, 1.36 g). The oil was diluted with ether (30 mL) and ethanol (5 mL), stirred for two 15 hours, and filtered to give the hydrochloride salt (0.21 g, 9% overall yield); m.p. = 112-113°C (no lit. value).

Mass spectrum: m/e: (CI). 140 ($\text{M-C}_5\text{H}_{11}$)⁺; 128 ($\text{M-C}_2\text{H}_3\text{N}_4$)⁺.

$^1\text{H-NMR}$ (D_2O , 300 MHz): 0.72 (t, 3H); 1.20 (d, 3H); 1.15-1.35 (m, 6H); 1.45/1.62 (2m, 1H each); 3.30 (t+m; 3H); 3.43 (m, 2H).

Elemental analysis: Calculated: %C = 48.47; %H = 8.95; %N = 28.27.

20 Found: %C = 48.24; %H = 8.85; %N = 28.40.

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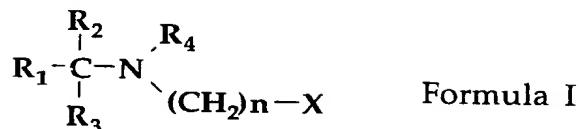
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WE CLAIM:

1. A compound of the Formula I



5 wherein:

R_1 is $(\text{CH}_2)_m\text{CH}_3$ where m is 0 or an integer in the range from 1 to 16, or an alkenyl, alkynyl, alkoxy, alkylthio, or alkyl sulfinyl group having from 2 to 17 carbon atoms,

R_2 = H, CH_3 or CH_2CH_3 ,

10 R_3 = H or CH_3 ,

R_4 = H or CH_3 ,

R_5 = lower alkyl having from 1 to 5 carbon atoms,

n is an integer in the range from 1 to 3,

15 and X is carboxyl (COOH) or carbalkoxy (COOR_5), cyano ($\text{C}\equiv\text{N}$), phosphonic acid (PO_3H_2), phosphonate ester ($\text{PO}_3[\text{R}_5]_2$) or 5-tetrazole, or a pharmaceutically acceptable salt thereof.

2. A compound of the Formula I according to claim 1 wherein:

R_1 = $(\text{CH}_2)_m\text{CH}_3$ where m is 0 or an integer in the range from 1 to 16,

R_2 = CH_3 ,

20 R_3 = H,

R_4 = H or CH_3 ,

R_5 = lower alkyl having from 1 to 5 carbon atoms,

n is an integer in the range from 1 to 3,

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and X is carboxyl (COOH) or carbalkoxy (COOR₅), cyano (C≡N), phosphonic acid (PO₃H₂), phosphonate ester (PO₃[R₅]₂) or 5-tetrazole, or a pharmaceutically acceptable salt thereof.

3. A compound of the Formula I according to claim 1 wherein:

5 R₁ = (CH₂)_mCH₃ where m is 0 or an integer in the range from 1 to 16,
R₂ = CH₃,
R₃ = H,
R₄ = H or CH₃,
R₅ = lower alkyl having from 1 to 5 carbon atoms,
10 n is an integer in the range from 1 to 3,
and X is carboxyl (COOH) or carbalkoxy (COOR₅) cyano (C≡N), phosphonic acid (PO₃H₂), phosphonate ester (PO₃[R₅]₂) or 5-tetrazole, as a substantially pure enantiomer in the R-configuration, or a pharmaceutically acceptable salt thereof.

15 4. A compound of the formula I according to claim 1 wherein:

R₁ = (CH₂)_mCH₃ where m is 0 or an integer in the range from 1 to 16,
R₂ = CH₃,
R₃ = H,
R₄ = H or CH₃,
20 R₅ = lower alkyl having from 1 to 5 carbon atoms,
n is an integer in the range from 1 to 3,
and X is carboxyl (COOH) or carbalkoxy (COOR₅) cyano (C≡N), phosphonic acid (PO₃H₂), phosphonate ester (PO₃[R₅]₂) or 5-tetrazole, as a substantially pure enantiomer in the S-configuration, or a pharmaceutically acceptable salt thereof.

25 5. A compound of the Formula I according to claim 1 wherein:

R₁ = (CH₂)_mCH₃ where m is 0 or an integer in the range from 1 to 16,

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$R_2 = CH_3$,

$R_3 = H$,

$R_4 = H$ or CH_3 ,

$R_5 =$ lower alkyl having from 1 to 5 carbon atoms,

5 n is an integer in the range from 1 to 3,

and X is carboxyl (COOH) or carbalkoxy (COOR₅), cyano (C≡N), phosphonic acid (PO₃H₂), phosphonate ester (PO₃[R₅]₂) or 5-tetrazole, wherein the compound is racemic or achiral and with the following exclusions:

a) for X = COOH; n = 1; $R_3 = R_4 = H$, exclude compounds for which:

10 $R_2 = H$ and m = 1 to 4, 6, 7, 9, 11, or 13, and

$R_2 = CH_3$ and m = 0, 1 or 2;

b) for X = COOH; n = 1; $R_3 = H$; $R_4 = CH_3$, exclude compounds for which:

$R_2 = H$ and m = 2 or 3, and

$R_2 = CH_3$ and m = 0;

15 c) for X = COOR₅; n = 1; $R_3 = R_4 = H$, exclude compounds for which:

$R_2 = H$ and m = 1 to 4, or 9, and

$R_2 = CH_3$ and m = 0 or 1, and

$R_5 =$ methyl, ethyl, t-butyl;

d) for X = COOH; n = 2; $R_3 = R_4 = H$, exclude compounds for which:

20 $R_2 = H$ and m = 1 to 4, 6, 9 or 11, and

$R_2 = CH_3$ and m = 0, 1 or 4;

e) for X = COOH; n = 2; $R_3 = H$; $R_4 = CH_3$, exclude compounds for which:

$R_2 = H$ and m = 1 or 2;

f) for X = COOR₅; n = 2; $R_3 = R_4 = H$, exclude compounds for which:

25 $R_2 = H$ and m = 1 to 5, 9 or 15,

$R_2 = CH_3$ and m = 0 or 1, and

$R_5 =$ methyl, ethyl, t-butyl;

g) for X = COOR₅; n = 2; $R_3 = H$; $R_4 = CH_3$, exclude compounds for which:

$R_2 = H$ and m = 1 or 2,

30 $R_2 = CH_3$ and m = 0, and

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R_5 = methyl, ethyl, t-butyl;

- h) for $X = COOH$; $n = 3$; $R_3 = R_4 = H$, exclude compounds for which:
 $R_2 = H$ and $m = 2$ or 6;
- i) for $X = COOR_5$; $n = 3$; $R_3 = R_4 = H$, exclude compounds for which:
 5 $R_2 = H$ and $m = 2$,
 $R_2 = CH_3$ and $m = 0$ or 1, and
 R_5 = methyl, ethyl, t-butyl;
- j) for $X = C\equiv N$ (cyano); $n = 1$; $R_3 = R_4 = H$, exclude compounds for
 which:
 10 $R_2 = H$ and $m = 1, 2, 4, 5$ or 6, and
 $R_2 = CH_3$ and $m = 0, 1$ or 2;
- k) for $X = C\equiv N$; $n = 1$; $R_3 = H$; $R_4 = CH_3$, exclude compounds for which:
 15 $R_2 = H$ and $m = 1$, and
 $R_2 = CH_3$ and $m = 0$;
- l) for $X = C\equiv N$; $n = 2$; $R_3 = R_4 = H$, exclude compounds for which:
 20 $R_2 = H$ and $m = 1, 2, 3, 4$ or 6, and
 $R_2 = CH_3$ and $m = 0, 1$ or 4;
- m) for $X = C\equiv N$; $n = 2$; $R_3 = H$; $R_4 = CH_3$, exclude compounds for which:
 25 $R_2 = H$ and $m = 2$, and
 $R_2 = CH_3$ and $m = 0$;
- n) for $X = C\equiv N$; $n = 3$; $R_3 = R_4 = H$, exclude compounds for which:
 30 $R_2 = H$ and $m = 1$ to 4, and
 $R_2 = CH_3$ and $m = 1$ or 2;
- o) for $X = PO_3H_2$; $n = 2$; $R_3 = R_4 = H$, exclude compounds for which:
 35 $R_2 = CH_3$ and $m = 0, 1$ or 5;
- p) for $X = PO_3(R_5)_2$; $n = 2$; $R_3 = R_4 = H$, exclude compounds for which:
 40 $R_2 = CH_3$ and $m = 0$ or 1, and
 R_5 = ethyl; and
- q) for $X = 5$ -tetrazole; $n = 2$; $R_3 = R_4 = H$, exclude compounds for which:

$R_2 = CH_3$ and $m = 0$.

6. A compound of the Formula I according to any one of claims 1 to 5 wherein R_1 is substituted with at least one of the substituents selected from hydroxy, aldehyde, oxo, lower acyloxy, halogen, thio, sulfoxide, sulfone, phenyl, halogen-substituted phenyl, hydroxy-substituted phenyl, cycloalkyl having from 3 to 6 carbon atoms and heterocyclic substituents having between 3 and 6 atoms, of which from 1 to 3 are heteroatoms selected from O, S and/or N.

7. A compound according to claim 3, wherein said compound of

10 formula I is selected from the group consisting of:

(R)-3-(2-Heptylamino)propionic acid;

(R)-3-(2-Heptylmethylamino)propionic acid;

Methyl (R)-3-(2-heptylamino)propionate;

Methyl (R)-3-(2-heptylmethylamino)propionate;

15 (R)-2-(2-Pentylamino)acetonitrile;

(R)-2-(2-Pentylmethylamino)acetonitrile;

(R)-3-(2-Heptylamino)propionitrile;

(R)-3-(2-Heptylmethylamino)propionitrile;

(R)-2-(2-Pentylamino)ethanephosphonic acid;

20 (R)-2-(2-Pentylmethylamino)ethanephosphonic acid; and

(R)-2-(2-Heptylamino)ethane-5-tetrazole.

8. A compound according to claim 4, wherein said compound of formula I is selected from the group consisting of:

(S)-2-(2-Heptylamino)acetic acid;

25 (S)-2-(2-Heptylmethylamino)acetic acid;

Methyl (S)-2-(2-heptylamino)acetate;

Methyl (S)-2-(2-heptylmethylamino)acetate;

(S)-2-(2-Heptylamino)acetonitrile;

(S)-2-(2-Heptylmethylamino)acetonitrile;

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(S)-2-(2-Heptylamino)ethanephosphonic acid; and
(S)-2-(2-Heptylmethylamino)ethanephosphonic acid.

9. A compound according to claim 5, wherein said compound of formula I is selected from the group consisting of:

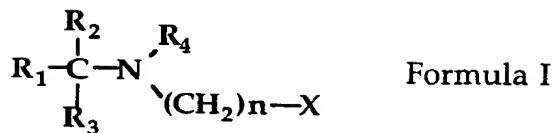
5 2-(1-Hexylmethylamino)acetic acid;
3-(2-Propylmethylamino)propionic acid;
Methyl 2-(2-propylmethylamino)acetate;
Methyl 2-(1-hexylmethylamino)acetate;
Methyl 3-(1-hexylmethylamino)propionate;
10 2-(1-Hexylamino)acetonitrile;
2-(1-Hexylmethylamino)acetonitrile;
3-(3-Pentylamino)propionitrile;
3-(3-Pentylmethylamino)propionitrile;
2-(2-Propylamino)ethanephosphonic acid; and
15 2-(2-Propylmethylamino)ethanephosphonic acid.

10. A compound according to any one of claims 1 to 9 in the form of a hydrochloride salt.

11. A compound according to any one of claims 3 to 9 wherein m is an integer from 1 to 12.

20 12. A compound according to any one of claims 3 to 9 wherein m is an integer from 1 to 9.

13. A composition for the treatment or prevention of a disease in which cell death occurs by apoptosis, which composition comprises an effective amount of a compound having the formula I:



wherein:

R_1 is $(\text{CH}_2)_m\text{CH}_3$ where m is 0 or an integer in the range from 1 to 16, or an

5 alkenyl, alkynyl, alkoxy, alkylthio, or alkyl sulfinyl group having from 2 to 17 carbon atoms,

$\text{R}_2 = \text{H}, \text{CH}_3$ or CH_2CH_3 ,

$\text{R}_3 = \text{H}$ or CH_3 ,

$\text{R}_4 = \text{H}$ or CH_3

10 $\text{R}_5 =$ lower alkyl having from 1 to 5 carbon atoms,

n is an integer in the range from 1 to 3,

and X is carboxyl (COOH), carbalkoxy (COOR_5), cyano ($\text{C}\equiv\text{N}$), phosphonic acid (PO_3H_2), phosphonate ester ($\text{PO}_3[\text{R}_5]_2$) or 5-tetrazole, or a pharmaceutically acceptable salt thereof, in admixture with a suitable

15 diluent or carrier.

14. A composition according to claim 13, wherein:

R_1 is $(\text{CH}_2)_m\text{CH}_3$ where m is 0 or an integer in the range from 1 to 16,

$\text{R}_2 = \text{CH}_3$,

$\text{R}_3 = \text{H}$,

20 $\text{R}_4 = \text{H}$ or CH_3 ,

$\text{R}_5 =$ lower alkyl having from 1 to 5 carbon atoms,

n is an integer in the range from 1 to 3,

and X is carboxyl (COOH), carbalkoxy (COOR_5), cyano ($\text{C}\equiv\text{N}$), phosphonic acid (PO_3H_2), phosphonate ester ($\text{PO}_3[\text{R}_5]_2$) or 5-tetrazole, or a

25 pharmaceutically acceptable salt thereof, in admixture with a suitable diluent or carrier.

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15. A composition according to claim 13 or 14, wherein R_1 differs from R_2 , $R_3 = H$ and the compound is in the R-configuration.

16. A composition according to claim 13 or 14, wherein R_1 differs from R_2 , $R_3 = H$ and the compound is in the S-configuration.

5 17. A composition according to any one of claims 13 to 16, wherein R_1 is substituted with at least one of the substituents selected from hydroxy, aldehyde, oxo, lower acyloxy, halogen, thio, sulfoxide, sulfone, phenyl, halogen-substituted phenyl, hydroxy-substituted phenyl, cycloalkyl having from 3 to 6 carbon atoms and heterocyclic substituents having between 3
10 and 6 atoms, of which from 1 to 3 are heteroatoms selected from O, S and/or N.

18. A composition according to claim 13 or 14, wherein said compound of formula I is selected from the group consisting of:

2-(2-Propylamino)acetic acid;

15 2-(1-Hexylamino)acetic acid;

(S)-2-(2-Heptylamino)acetic acid;

3-(2-Propylamino)propionic acid;

3-(1-Hexylamino)propionic acid;

(R)-3-(2-Heptylamino)propionic acid;

20 2-(2-Propylmethylamino)acetic acid;

2-(1-Hexylmethylamino)acetic acid;

(S)-2-(2-Heptylmethylamino)acetic acid;

3-(2-Propylmethylamino)propionic acid;

3-(1-Hexylmethylamino)propionic acid;

25 (R)-3-(2-Heptylmethylamino)propionic acid;

2-(2-Propylamino)acetonitrile;

(R)-2-(2-Pentylamino)acetonitrile;

2-(1-Hexylamino)acetonitrile;

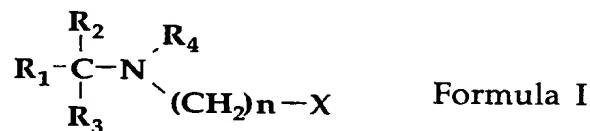
(S)-2-(2-Heptylamino)acetonitrile;

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(R)-3-(2-Heptylamino)propionitrile;
 2-(2-Propylmethylamino)acetonitrile;
 (R)-2-(2-Pentylmethylamino)acetonitrile;
 2-(1-Hexylmethylamino)acetonitrile;
 5 (S)-2-(2-Heptylmethylamino)acetonitrile;
 (R)-3-(2-Heptylmethylamino)propionitrile;
 2-(2-Propylamino)ethanephosphonic acid;
 (R)-2-(2-Pentylamino)ethanephosphonic acid;
 (S)-2-(2-Heptylamino)ethanephosphonic acid;
 10 2-(2-Propylmethylamino)ethanephosphonic acid;
 (S)-2-(2-Heptylmethylamino)ethanephosphonic acid; and
 (R)-2-(2-Heptylamino)ethane-5-tetrazole.

19. A composition according to claim 18, wherein the compound of formula I is in the form of a hydrochloride salt.

15 20. A use of a compound of the formula I for the treatment or prevention of a disease in which cell death occurs by apoptosis, wherein said compound has the formula I:



20 wherein:

R₁ is (CH₂)_mCH₃ where m is 0 or an integer in the range from 1 to 16, or an alkenyl, alkynyl, alkoxy, alkylthio, or alkyl sulfinyl group having from 2 to 17 carbon atoms,

R₂ = H, CH₃ or CH₂CH₃

25 R₃ = H or CH₃

R₄ = H or CH₃

R₅ = lower alkyl having 1 to 5 carbon atoms

n is an integer in the range from 1 to 3,
and X is carboxyl (COOH), carbalkoxy (COOR₅), cyano (C≡N), phosphonic acid (PO₃H₂), phosphonate ester (PO₃[R₅]₂) or 5-tetrazole, or a pharmaceutically acceptable salt thereof.

5 21. A use according to claim 20, wherein
R₁ is (CH₂)_mCH₃ where m is 0 or an integer in the range from 1 to 16,
R₂ = CH₃,
R₃ = H,
R₄ = H or CH₃,
10 R₅ = lower alkyl having 1 to 5 carbon atoms,
n is an integer in the range from 1 to 3,
and X is carboxyl (COOH), carbalkoxy (COOR₅), cyano (C≡N), phosphonic acid (PO₃H₂), phosphonate ester (PO₃[R₅]₂) or 5-tetrazole, or a pharmaceutically acceptable salt thereof.

15 22. A use according to claim 20 or 21 wherein R₁ is substituted with at least one of the substituents selected from hydroxy, aldehyde, oxo, lower acyloxy, halogen, thio, sulfoxide, sulfone, phenyl, halogen-substituted phenyl, hydroxy-substituted phenyl, cycloalkyl having from 3 to 6 carbon atoms and heterocyclic substituents having between 3 and 6 atoms, of which 20 from 1 to 3 are heteroatoms selected from O, S and/or N.

23. A use according to claim 20 wherein said compound of Formula I is selected from the group consisting of:
2-(2-Propylamino)acetic acid;
2-(1-Hexylamino)acetic acid;
25 (S)-2-(2-Heptylamino)acetic acid;
3-(2-Propylamino)propionic acid;
3-(1-Hexylamino)propionic acid;
(R)-3-(2-Heptylamino)propionic acid;

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2-(2-Propylmethylamino)acetic acid;
2-(1-Hexylmethylamino)acetic acid;
(S)-2-(2-Heptylmethylamino)acetic acid;
3-(2-Propylmethylamino)propionic acid;
5 3-(1-Hexylmethylamino)propionic acid;
(R)-3-(2-Heptylmethylamino)propionic acid;
2-(2-Propylamino)acetonitrile;
(R)-2-(2-Pentylamino)acetonitrile;
2-(1-Hexylamino)acetonitrile;
10 (S)-2-(2-Heptylamino)acetonitrile;
(R)-3-(2-Heptylamino)propionitrile;
2-(2-Propylmethylamino)acetonitrile;
(R)-2-(2-Pentylmethylamino)acetonitrile;
2-(1-Hexylmethylamino)acetonitrile;
15 (S)-2-(2-Heptylmethylamino)acetonitrile;
(R)-3-(2-Heptylmethylamino)propionitrile;
2-(2-Propylamino)ethanephosphonic acid;
(R)-2-(2-Pentylamino)ethanephosphonic acid;
(S)-2-(2-Heptylamino)ethanephosphonic acid;
20 2-(2-Propylmethylamino)ethanephosphonic acid;
(S)-2-(2-Heptylmethylamino)ethanephosphonic acid; and
(R)-2-(2-Heptylamino)ethane-5-tetrazole.

24. A use according to any one of claims 20 to 23 wherein the disease is selected from the group consisting of stroke, head trauma, Bell's palsy, spinal cord injury, Alzheimer's disease, Parkinson's disease, Pick's disease, amyotrophic lateral sclerosis, Huntington's disease, multiple sclerosis, cardiac myopathies, nephropathy, retinopathy, diabetic complications, glaucoma and idiopathic neuropathies.

25. A use according to any one of claims 20 to 24, for the treatment
30 of a human.

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26. A commercial package for the treatment or prevention of a disease in which cell death occurs by apoptosis, said package comprising a pharmaceutical composition according to any one of claims 13 to 19, together with instructions for use in the treatment or prevention of diseases
5 in which cell death occurs by apoptosis.